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CARCINOMA OF THE CORPUS UTERI

End-Results of Treatment in 531 Cases from 1926–19

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CANCER of the uterus, according to Bureau of Census statistics, caused the death in 1942 of 16,393 American women. Carcinoma of the endometrium is probably responsible for a fifth or more of these deaths, since the ratio of corpus to cervical carcinoma has been variously estimated by different writers as: 1 to 2.4 (10), 1 to 3.4 (19), 1 to 4.5 (18), and 1 to 8.2 (17). The importance of corpus carcinoma has been underestimated, partly because of its supposed infrequency, partly because of the persistent belief in its good prognosis.

Statistics on the results of the treatment of corpus carcinoma are partly responsible for the misconception about this disease. Methods of reporting cases of carcinoma of the corpus have never been standardized, as they have, for instance, for cervical cancer. Too many reports have been based on cases selected for special treatment and the statistical principle of showing the results upon all cases applying to a given institute for treatment has not been followed. In the analysis of the cases to follow, the attempt is to be made, with the aid of data from several contributions in the literature, to answer certain questions about cancer of the corpus.

The series to be reported includes all histologically proved cases of carcinoma of the corpus uteri in patients admitted to the Memorial Hospital during the 15 year period from 1926 to 1940.[1] Only 7 patients are excluded, 5 who refused treatment and 2 who were referred back to the institution that had initiated treatment. Of the 531 patients considered, 368 had received no treatment prior to their admission to the Memorial Hospital and will be referred to as "primary" cases; 163 had received previous treatment elsewhere and will be termed "secondary" cases.

This report is concerned primarily with end-results. Etiologic factors such as age incidence, parity, marital status and the menopause, and symptomatology will be referred to only briefly. Pathology and therapy will be discussed in relation to end-results.

ETIOLOGIC FACTORS

Age. The average age for the group of primary cases was 57.4 years, the standard deviation from the mean 8.8 years. The youngest patient was 30 years old and the oldest 79. The 5 year period of greatest incidence was 60 to 64, and 42 per cent of the patients fall in the decade between 55 and 64 years of age. The age distribution by 5 year periods is presented in Table I.

Marital status. Of the patients on whom data were available 88.5 per cent were mar-

From the Gynecological Division of the Memorial Hospital, New York.

[1]These patients were treated under the immediate direction of Dr. William P. Healy who was in charge of the Gynecological Division during the years of this report.

TABLE I.—AGE DISTRIBUTION

Age group	Number	Per cent
30 – 34 years	4	1.1
35 – 39	11	2.9
40 – 44	14	3.8
45 – 49	41	11.0
50 – 54	68	18.2
55 – 59	72	19.3
60 – 64	85	22.8
65 – 69	56	15.0
70 and older	22	5.9
Total	373	100.0

ried or widowed; 11.5 per cent had never married. The figure for the single women does not differ greatly from that of a United States Census report which stated that in 1940, in the New York-Northeastern New Jersey Metropolitan area, 12.1 per cent of women over 35 were unmarried (22). A report by the British Clinical Cancer Research Committee (1) in 1941, which compared the ratios of married and widowed to single women among the patients suffering from cancer with that to be expected among living women at separate age groups, showed that the liability to carcinoma of the corpus is somewhat less among married and widowed than among single women. Pack and LeFevre noted that the percentage of single women with cancer of the body of the uterus was four times as great as the percentage of single women with carcinoma of the cervix.

Parity. The parity was recorded in the histories of 461 patients. Of these, 31.5 per cent had never conceived, and all the pregnancies of 3.9 per cent had ended in abortion; that is, 35.4 per cent had never had a full term pregnancy. In 1940 in the New York-Northeastern New Jersey Metropolitan area, of women 35 years old and over who had ever married, 16.7 per cent had never borne a child (22). The statistics in the Memorial Hospital series indicate, then, that women destined to develop corpus cancer marry with about the normal frequency but then exhibit a relatively high degree of infertility.[1]

[1]While the 1930 population, for which figures are not available, would be a more suitable comparison year, the proportions of single and childless women in 1940 are presumably at least as great as in 1930. Consequently, differences between the corpus series and the comparison population will be underestimated rather than overestimated. Mrs. Ruth F. Salt, biometrician in the Statistics Department at Memorial Hospital, points out that the true differences between women with cancer of the corpus and women in the general population cannot be determined until groups of similar age, income level, education, age at marriage, occupation of spouse, etc., are compared. Death rates from cancer of the corpus for single, married, parous and nonparous women should also be compared.

TABLE II.—ONSET OF SYMPTOMS IN RELATION TO THE MENOPAUSE

	Number	Per cent
Menopause not yet reached	98	21.17
Menopause was artificially induced	23	4.97
Patient past the menopause	342	73.86

Average age of natural menopause—48.5 years

Menopause. The average age of the natural menopause was 48.5 years. As indicated in Table II, 73.86 per cent of the patients were in the postmenopausal period, 21.17 per cent had not yet reached the menopause, and there had been an artificially induced menopause in 4.97 per cent of the cases. Data were lacking on 12.8 per cent of the patients.

Associated primary carcinomas. Twenty-two of the patients had more than one primary carcinoma, making the incidence of double primaries 4 per cent. The frequency with which the other primary carcinomas occurred in particular sites was as follows: breast, 11; cervix, 3; vulva, 2; large bowel, 2; kidney, 1; esophagus, 1; bladder, 1; and lymphosarcoma, 1. Warren and Gates reported an incidence of 3.7 per cent in their series of 1,078 cancer autopsies. Hurt and Broders found that the frequency of multiple primary tumors among 2,124 patients with malignant tumors treated at the Mayo Clinic in the calendar year 1929 was 3.34 per cent. Among the 2,124 patients studied by Hurt and Broders, there were 71 cases of multiple malignant lesions. There were 8 cases of endometrial adenocarcinoma, and in every instance the associated lesion was in the breast or genitalia.

SYMPTOMATOLOGY

Vaginal bleeding was a symptom in 96.6 per cent of the cases, but was usually slight, characterized by the patient as "staining" or "spotting." In those women who had not yet reached the menopause, menorrhagia of many years' duration was not an uncommon complaint although more often the bleeding was of the intermenstrual type. The commonest picture of all was, of course, postmenopausal bleeding. An associated vaginal discharge was mentioned in the histories of 57 per cent of the cases. Twenty-two per cent of the patients were complaining of pain at the time of admission to the hospital.

TABLE III.—RELATION OF DURATION OF SYMPTOMS TO END-RESULTS

Duration of symptoms in months	Cases Number	Cases Per cent	Five year cures Number	Five year cures Per cent
Less than 6	125	35.92	48	38.4
6 – 11	82	23.56	33	40.2
12 – 23	65	18.68	27	41.6
24 – 35	33	9.48	13	39.4
36 – 47	16	4.59	8	50.0
48 – 59	7	2.01	2	28.6
60 or more	20	5.76	10	50.0
Total	348	100.00	141	40.5

The average duration of symptoms before treatment for the primary cases was 15 months. The histories tend to confirm the opinion that carcinoma of the corpus uteri is often slow in growth and may extend beyond the uterus only after many months or years. Yet there was evidently great variability in this respect. Several of the patients who had disease in an advanced stage had experienced symptoms for only a few days, while many of those whose symptoms were of several years' duration were found to have a normal sized uterus with the cancer still confined to that organ.

It was surprising also that, at least in this series, there was no evidence that the failure of treatment was directly related to the length of the symptoms. The relative success in the group of cases of long duration suggests the possibility that in some of these at least the endometrial lesion was in the beginning a benign one. Several studies have presented evidence that hyperplasia of the endometrium may be a predisposing factor to the later development of cancer. The literature also contains reports of several instances of apparent transformation of hyperplasia into carcinoma, as indicated by a change in the character of the tissue obtained in successive curettings in the same patient.

THE END-RESULTS IN CARCINOMA OF THE CORPUS

The end-results of the treatment of all patients with histologically verified carcinoma of the uterine fundus admitted to Memorial Hospital during the period 1926 to 1940 inclusive are summarized in Table IV.

At the Memorial Hospital, all of the ward patients and a majority of the private patients are treated by members of the gynecologic division. About a tenth of all cases, however, are managed as private cases by attendants from other divisions. For completeness, it has seemed necessary to present figures for the entire hospital but, since only the cases of the gynecologic division could be supervised from a standpoint of technique, it was also necessary to report figures for this group separately. In most of the following tables, therefore, two groups of figures appear, those for the whole hospital and those for the gynecologic division. In general, however, there is no significant difference between results in the two groups.

Of the 531 patients, 483 were clinic and private patients treated on the gynecologic division; the remaining 48 were private patients under the care of attending surgeons on other services.

Of the 531 patients, 368, or 69.3 per cent of the patients, received all of their treatment

TABLE IV.—END-RESULTS FOR ALL CASES 1926 – 1940

	Memorial Hospital	Gynecologic Division
Total number of cases	531	483
Indeterminate group		
Dead as a result of other causes and without recurrence	32	31
Lost track of without recurrence	25	15
Total number of indeterminate results	57	46
Determinate group		
Total number minus those of indeterminate group	474	437
Failures		
Dead as a result of carcinoma or its treatment	245	230
Lost track of with cancer (probably dead)	10	8
Living with recurrence	17	16
Total number of failures in treatment	272	254
Successful results		
Free of carcinoma after 5 years	202	183
Five-year end-results		
Successful results divided by determinate group	(202/474) 42.6%	(183/437) 41.9%
Absolute cure rate		
Successful results divided by total number of cases	(202/531) 38.0%	(183/483) 37.9%

A total of 52 cases seen in the Memorial Hospital during these years were excluded from consideration because, although probably carcinoma of the corpus, there was no histologic proof. Of this group, 7 refused treatment and 1 was referred back to the institution which had begun treatment.

Among the 14 primary cases treated without histologic proof, there were no cures. Among the 30 secondary cases, there were 6 cures after 5 years.

TABLE V.—END-RESULTS FOR PRIMARY CASES 1926 – 1940

	Memorial Hospital	Gynecologic Division
Total number of primary cases	368	336
Indeterminate group Dead as a result of other causes and without recurrence	21	20
Lost track of without recurrence	18	10
Total number of indeterminate results	39	30
Determinate group Total number minus those of indeterminate group	329	306
Failures Dead as a result of carcinoma or its treatment	168	159
Lost track of with cancer (probably dead)	5	3
Living with recurrence	9	8
Total number of failures in treatment	182	170
Successful results Free of carcinoma after 5 years or more	147	136
Five year end-results Successful results divided by determinate group	(147/329) 44.7%	(136/306) 44.4%
Absolute cure rate Successful results divided by total number of cases	(147/368) 39.9%	(136/336) 40.5%

here; 163 or 30.7 per cent had undergone some treatment prior to their admission to the Memorial Hospital.

The *absolute five year cure rate for the entire series*, including both primary and secondary cases, was 38 per cent. The 57 patients who died of other causes and without clinical evidence of recurrence and the patients who were lost track of without recurrence were considered failures in treatment.

END-RESULTS IN PRIMARY CARCINOMA OF THE CORPUS

In Table V, constructed according to a standard form in use for the reporting of end-results at the Memorial Hospital, are shown the results in the 368 primary cases.

In this group, there were 147 five year cures, giving an absolute cure rate of about 40 per cent (39.9). Since in this age group there is a considerable death rate from unrelated causes, a perhaps truer picture of the prognosis is given by accepting the figures for the "determinate cases," after subtracting the cases lost

TABLE VI.—RELATION OF CLINICAL GROUP TO END-RESULTS PRIMARY CASES ON GYNECOLOGIC DIVISION

Clinical group	Cases Number	Cases Per cent	Five year cures Number	Five year cures Per cent
Clinical Group I Uterus not enlarged....	50	15.10	33	66.6
Clinical Group II A Uterus not larger than 2½ months' gestation..	136	41.09	74	54.4
Clinical Group II B Uterus larger than 2½ months' gestation..	29	8.76	11	37.9
Clinical Group III A Extension of carcinoma to cervix only.....	37	11.18	9	24.3
Clinical Group III B Extension of carcinoma beyond uterus.....	79	23.87	9	11.2
All Cases.....	331*	100.00	136	41.1

*The records of 5 patients contained no data relative to clinical group.

track of without evidence of cancer and those dying of intercurrent illness. The effect of this correction is, however, only to raise the apparent cure rate to about 45 per cent.

The relationship of clinical extent of disease to end-results. A slight modification of Healy's (8) classification based on the palpable size of the uterus and the extent of disease at first examination was employed in dividing the primary cases into three clinical groups. This classification, which appears a highly practical one, is as follows:

Group I. Those cases in which there is no palpable evidence of uterine enlargement or extension of disease beyond the fundus.

Group II. Those cases showing uterine enlargement without fixation or other evidence of carcinoma elsewhere. This group was subdivided into Group IIA in which were placed those patients in whom the uterus was larger than a 2½ months' gestation, and Group IIB which included patients whose uterus was larger than a 2½ months' gestation but still freely movable.

Group III. Patients exhibiting clinical signs of extension of cancer beyond the uterine fundus itself. Group III was further subdivided into those relatively favorable cases in which cancer had extended to the cervix only, and into another group showing evidence of extension beyond the uterus into the vagina, parametria, and adnexa, and distant metastases.

The practical importance of this clinical classification is demonstrated in Table VI which

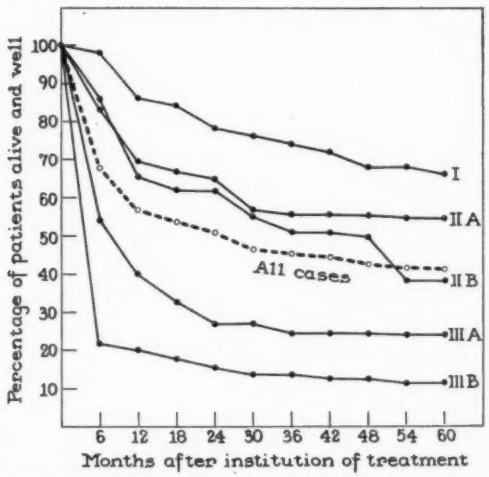
shows the relation of the clinical extent of disease to end-results. Of the 50 patients in Group I, 66.6 per cent were alive and free of disease for 5 years or more. The absolute 5 year cure rate for the 136 patients with uteri enlarged up to the size of a 2½ months' gestation was 54.4 per cent. In 29 cases the uterine enlargement was greater than a 2½ months' gestation and only 37.9 per cent were 5 year cures. There were 37 patients in Group IIIA, 24.3 per cent of whom were living without evidence of recurrence at the end of 5 years. In Group IIIB were placed 79 patients with clinical evidence of extension of cancer beyond the uterus; the absolute cure rate in this group was only 11.2 per cent.

A similar plan of clinical division based on the size of the uterus was followed by Miller. His cases were divided into 3 clinical groups with the uterus normal in size in the first group, enlarged to the size of a 2½ months' pregnancy in the second, and to a 3 months' pregnancy in the third. The percentages of survival in these groups were 66, 56, and 23, respectively, while, had we used the same classification, our corresponding figures would have been 66, 54, and 26.

The importance of the clinical extent of the disease is shown again in Graph 1 where the percentage of surviving patients is plotted at each 6 month interval after treatment was initiated. The survival curves show that the unfavorable prognosis of the more advanced cases is due especially to immediate deaths within the first 6 to 12 months after treatment. When a patient has survived the first 12 months without recurrence, her chance of survival is quite good regardless of her original condition. The survival curve is presented in the belief that it may be of aid in explaining the chances of cure to the anxious and often confused members of the families of patients with cancer of the corpus.

The relationship of histologic type to end-results. In accordance with a plan previously employed in reporting carcinoma of the corpus from this hospital (Healy and Brown, 8), the 368 cases were divided on a histologic basis into 4 groups (Table VII).

Group A—adenocarcinoma, grades I and II. This group included also cases originally diagnosed as "adenoma malignum," a term now regarded as undesirable. Of the 199 cases with these relatively differentiated tumors, the absolute 5 year cure rate was 47.2 per cent. When only cases of "adenoma malignum" are considered, the figure becomes approximately 51 per cent.



Graph 1. Relation of clinical extent of disease to end-results in primary cases of carcinoma of corpus uteri.

Group B—adenocarcinoma, grades III and IV and "embryonal" carcinoma. Of these undifferentiated tumors, there were 117 cases with a 5 year absolute cure rate of 22.8 per cent, a figure less than half of the preceding group.

Group C—adenoacanthoma. The results in this interesting histologic variety showed a cure rate of 51.3 per cent among the 37 cases, suggesting that squamous metaplasia tends to occur in relatively differentiated growths.

Group D — miscellaneous. In this group were placed 15 cases in which inadequate microscopic preparation made classification on this basis impossible.

It appears evident that the prognosis in endometrial cancer is strongly affected by the degree of differentiation of the tumor. This is in accord with a number of previous reports (Healy and Brown, 8; Taylor, etc.).

The unfavorable prognosis of the less differentiated tumors may depend on one or both of two possibilities. First, the grades III and

TABLE VII.—RELATION OF HISTOLOGIC TYPE TO END-RESULTS

Histologic type	Number of cases	Per cent of total	Five year cures Number	Five year cures Per cent
Adenocarcinoma, grades I and II	199	54.08	94	47.2
Adenocarcinoma, grades III and IV and embryonal adenocarcinoma	117	31.79	29	22.8
Adenoacanthoma	37	10.05	19	51.3
Miscellaneous	15	4.08	5	33.3
Total	368	100.00	147	39.9

IV may be more fatal on account of a greater tendency to metastasize, even when the original tumors are grossly of equal size. Second, a greater rapidity of initial growth may have produced at the time of treatment a larger primary tumor and so affect prognosis simply on the basis of a more extensive local disease.

Table VIII shows that the second possibility is at least one of the factors. In clinical Group I only 14 per cent of the cases are of the undifferentiated types, whereas in the more extensive lesions these histologic types are several times as frequent.

The relationship of the type of treatment to end-results. The determination of the best method of treating carcinoma of the corpus has evaded statistical analysis. Nor has it been possible on the basis of this series to offer any final answer as to whether surgery alone or in some combination with radium or x-ray is most effective.

In all series, certainly in our own, cases are selected for a special form of therapy on the basis of factors which themselves affect the end-results. Of the most importance is the tendency to assign the patient who is a bad surgical risk, on account of obesity, age, or organic disease, to a program of radiation therapy. Such patients give less than the average

TABLE VIII.—RELATION OF HISTOLOGIC TYPE TO CLINICAL GROUP

	Group I Per cent	Group II A Per cent	Group II B Per cent	Group III A Per cent	Group III B Per cent
Adenocarcinoma, grades I and II	80.70	58.42	43.33	49.99	40.73
Adenocarcinoma, grades III and IV and embryonal adenocarcinoma	14.03	29.25	46.66	42.11	38.27
Adenoacanthoma	3.51	10.88	10.00	7.89	8.64
Miscellaneous	1.75	1.35	0.00	0.0	12.34

results among radiated just as they would among surgically treated cases.

Some favorable selection for surgery is seen in the tendency to omit radiation in the very early or unsuspected cases of endometrial cancer in order to prevent the patient's discovery of the diagnosis. Some cases having a bad outlook are, however, added to the surgical group in the belief that the very bulky uterus is too large for any significant effect from intracavitary radium.

In general, the individualization of treatment in cases of corpus cancer appears to favor the statistics for hysterectomy alone or in combination with radiation as opposed to a program depending exclusively on radiation therapy.

In reporting the effect of treatment on the Memorial series, the question of surgery, radium and x-ray will be considered first upon the entire series, then with relation to the clinical extent of the disease and finally to the histologic type of tumor.

A few points may be noted about the techniques employed with the various therapeutic measures.

1. Radium: The standard method of treatment has been the intrauterine application of a straight applicator containing radium, individually constructed for each case so as to extend from the external os to the top of the uterine cavity. The usual initial dose has been 3600 millicurie hours. Patients to have surgery are admitted for hysterectomy 6 weeks after the radium treatment. Patients in whom surgery is contraindicated and for whom it is hoped radiation will suffice are now recurretted after a 4 month interval and further radium inserted or the risk of a hysterectomy is then accepted if cancer is still present. In the earlier part of the period reported, however, patients treated by radiation alone were simply observed unless bleeding recurred.

2. X-ray: Roentgen therapy was at first given with massive doses of 750 r each to 4 or 6 portals (14 by 21 cm.) using a 200 kilovolt machine at 70 centimeters with 0.5 millimeter copper filtration. More recently, 250 kilovolt roentgen rays have been used, still with 4 to 6 pelvic ports, but with a divided dose, each field receiving 8 treatments of 250 r each. Roentgen therapy is now given rou-

tinely after the radium in patients treated by radiation only and less regularly after hysterectomy, but in the years of the series being reported x-ray, when given, was almost without exception the initial therapeutic procedure.

3. Surgery: The surgical operation employed has almost without exception been a total abdominal hysterectomy with removal of both adnexa. The cervix has been removed with only a small cuff of vagina and no attempt has been made to dissect out the lymph nodes or parametria.

In Table IX are presented the 5 year end-results according to the method of treatment without regard to stage of the disease or histologic type. The figures are, at first glance, entirely in favor of the surgically treated cases. This is best shown by the figures in the summary, indicating that of all cases in which a hysterectomy was performed, 51.1 per cent survived 5 years without recurrence, whereas among the cases with treatment limited to radium, with or without x-ray, only 36.8 were alive and well after 5 years.

Perhaps the best evidence for the need of a hysterectomy is the frequency with which residual viable cancer is found in excised uteri following large doses of preoperative irradiation. Of the 119 patients of this series who were subjected to hysterectomy, after having received as a rule 3600 millicurie hours of intrauterine radium, 59, or 49.6 per cent, had microscopic evidence of viable cancer in the excised uterus. The absolute 5 year cure rate in the cases without residual carcinoma in the irradiated excised uterus was 73.8 per cent while only 44.1 per cent of the patients whose uterus harbored residual cancer survived 5 years.

Among 70 of the patients recently reported by Corscaden, treated by hysterectomy after intrauterine application of radium, residual carcinoma was found in 50 per cent of the uteri. The possibility remains that an applicator more perfectly adapted to the varying sizes and shapes of the uterine cavity might result in a destruction of the carcinoma in a higher percentage of the cases treated.

Treatment in relation to the clinical stage. Further analysis of the series, by dividing into stages according to the gross extension of the disease, the cases in which patients were treated by each method shows that a more difficult group was assigned to radiation than to surgery (Table X).

TABLE IX.—RELATION OF TREATMENT TO END RESULTS

Method of treatment	Number of cases	Number of 5 year cures	Percentage of 5 year cures
Radium alone	60	28	46.7
Radium and x-ray	122	39	32.0
X-ray alone	10	0	00.0
Hysterectomy and radium	31	20	64.5
Hysterectomy, radium and x-ray	74	33	44.6
Hysterectomy and x-ray	13	5	38.4
Hysterectomy alone	17	11	64.7
Summary			
All patients treated by hysterectomy	135	169	51.1
Radium with or without x-ray	182	67	36.8

From Table XI, a condensation of Table X, it is evident that in the radium group there was twice the proportion of very advanced cases, a difference in selection which might easily account for the difference in total end-results.

The better comparison is perhaps made by studying the results only in the clinical groups I, IIA, and IIB, which may be regarded as technically operable. There were 109 such operable patients treated by irradiation alone, with an absolute 5 year cure rate of 52.3 per cent. A combination of irradiation and hysterectomy was used in the treatment of 90 similar cases with a cure rate of 56.6 per cent. Sixteen patients were treated by hysterectomy alone, of whom 10, or 60.3 per cent, survived for 5 years. These differences are probably not statistically significant and it becomes difficult to explain why, when surgical specimens so frequently show persistent cancer after radium, that the difference in cure rates among operable cases is not greater.

A greater contrast between surgically treated and radiated patients was recently reported by Corscaden, in a report based upon 27 cases in which patients were technically operable and were treated by the intrauterine application of radium, and 25 similar cases in which patients were treated by a combination of irradiation and hysterectomy. The 5 year survival rates in the 2 groups of cases were 48 per cent and

TABLE X.—RELATION OF CLINICAL GROUP AND METHOD OF TREATMENT TO END-RESULTS—PRIMARY CASES ON GYNECOLOGIC DIVISION

Method of treatment	Clinical group I			Clinical group II A			Clinical group II B			Clinical group III A			Clinical group III B		
	No. of cases	5 year cures		No. of cases	5 year cures		No. of cases	5 year cures		No. of cases	5 year cures		No. of cases	5 year cures	
		No.	%		No.	%		No.	%		No.	%		No.	%
Radium alone	15	11	73.3	26	15	57.7	5	2	40.0	6	0	00.0	8	0	00.0
Radium and x-ray	9	5	55.5	48	23	47.9	5	1	20.0	20	6	30.0	40	4	10.0
X-ray alone	0	0	00.0	1	0	00.0	0	0	00.0	0	0	00.0	9	0	00.0
Radium and hysterectomy	11	9	81.8	16	10	62.5	1	0	00.0	2	1	50.0	1	0	00.0
Radium and x-ray and hysterectomy	10	5	50.0	36	19	52.8	7	3	42.9	9	2	22.2	12	4	33.3
Hysterectomy alone	2	1	50.0	7	6	85.7	7	3	42.9	0	0	00.0	1	1	100.0
Hysterectomy and x-ray	3	2	66.6	2	1	50.0	4	2	50.0	0	0	00.0	4	0	00.0
Total	50	33	66.6	136	74	54.4	29	11	37.9	37	9	24.3	75*	9	11.2

*Three group III B cases were too far advanced for treatment but were included.

72 per cent respectively. Arneson collected from the literature a series of 473 cases in which patients were operable and were treated by radiation alone, and found that 53 per cent survived for 5 years.

Another important subject is the possible advantage of combining radiation with surgery in cases of carcinoma of the corpus in the hope of improving the results obtained by hysterectomy alone. Only 17 patients in this series were treated by surgery without radiation and these afford an insufficient control. The results on these few cases were, however, as good as in any group in which radiation was given in addition to surgery.

Review of several reports in the literature (Table XII) also fails to demonstrate a consistent effect on statistics when radiation is added to surgical treatment. Altogether it seems unproved that the cure rate in corpus cancer is being improved by preoperative or postoperative x-ray or radium.

Treatment in relation to histologic type. The bearing of histologic type upon method of treatment has been studied and the analysis of the series for this aspect is shown in Table XIII. A point of possible significance is the decided advantage evident when surgery is employed for the differentiated forms of cancer. For the adenocarcinoma of grades III and IV, however, the results for radiation alone appear to be as good as for surgery. It is possible that the radiosensitivity of these types is the determining factor and that metastasis has occurred so frequently by the time treatment is instituted that the removal of the uterus is a relatively unimportant step. The evidence for this special point is, however, still too fragmentary to base treatment upon it as a principle.

TABLE XI.—RELATION OF CLINICAL GROUP AND METHOD OF TREATMENT TO END-RESULTS

	Total cases	Stage I	Stage II A and II B	Stage III A and III B
Radium with or without x-ray.....	182	13.2	46.1	40.7
Hysterectomy, with or without radiation....	135	19.2	59.3	21.5

END-RESULTS IN PREVIOUSLY TREATED PATIENTS

The problem of the treatment of recurrent carcinoma of the corpus requires in itself a major study, and it is accordingly intended to report the secondary cases in only enough detail to make this a complete statistical study of the work of the hospital on carcinoma of the endometrium.

One hundred and sixty-three patients who had received prior treatment for corpus carcinoma were admitted to the Memorial Hospital during the 15 years under consideration (see Table XIV). Thirty of these women presented no clinical evidence of carcinoma on

TABLE XII.—RELATION OF METHOD OF TREATMENT TO END-RESULTS—RESULTS REPORTED BY OTHER AUTHORS

Author	Operation			Irradiation			Irradiation and operation			Totals		
	Cases	Alive 5 years	Per cent	Cases	Alive 5 years	Per cent	Cases	Alive 5 years	Per cent	Cases	Alive 5 years	Per cent
Burnam, 1931	7	3	50.0	82	21	25.6	9	5	45.5	97	29	29.9
Masson, 1934	331	193	58.3	161	32	19.8	150	87	58.0	642	312	48.6
Norris (16), 1934	5	3	60.0	28	15	53.5	15	10	66.6	49	28	57.1
Healy (6), 1934				18	18	100.0	29	22	75.9	47	40	85.0
Newell and Crossen, 1935	20	13	65.0	13	2	15.2	20	14	60.8	56	29	51.7
Beattie, 1933	12	9	75.0	15	3	18.0	8	2	25.0	35	14	40.0
Norris and Dunne (16), 1936	115	55	47.8	89	39	43.8				211	94	44.5
Healy (7), 1936										217	78	35.9
Arneson, 1936	20	13	65.0	18	5	28.0	10	9	90.0	48	27	56.2
Collection of Arneson (2), 1936	937	530	57.0	998	372	37.0	91	55	60.0	2016	957	47.4
Morton, 1937	13	9	69.2	24	9	37.5	18	12	66.6	62	33	53.2
Taylor and Becker, 1945 (includes only patients receiving all their treatment at Memorial Hospital)	19	11	57.9	213	70	32.8	126	66	52.4	358	147	41.0

admission, and the diagnosis was confirmed only by the microscopic examination of the material submitted from the institution at which treatment had been initiated. These were classed as "prophylactic" cases. The remaining 133 patients were termed "recurrent" cases since it was possible to make a diagnosis on biopsied or curetted tissue obtained after their admission to this hospital. No attempt was made to differentiate between "persistent" and "recurrent" disease.

The standard table for reporting end-results is given for completeness for all secondary cases (Table XIV). Nevertheless, the 2 groups have a decidedly different significance and require separate comment (Table XV).

a. The prophylactic group. Twenty of the 30 patients in the prophylactic group were alive and free of disease after 5 years—an absolute cure rate of 66.6 per cent. This is the figure which may be anticipated in any series of operable cases which are treated by hysterectomy.

b. The total recurrent group. This group of patients treated for the first time in other institutions and referred to the Memorial Hospital with cancer still present is a miscellaneous one. It includes the inoperable patients with fixed uteri and large abdominal masses, recurrences in the vaginal vault and about the hymenal ring and urethra, and finally cancer redeveloping in cervical stumps. There were 33 five year cures among the 133 recurrent cases, an absolute cure rate of 24.8 per cent. This figure indicates that even when the first effort at cure is a failure, some hope still exists for control of the disease.

One point in regard to the recurrent group is worth noting. Among the 90 patients who

TABLE XIII.—RELATION OF HISTOLOGIC TYPE TO END-RESULTS WITH RADIATION ALONE AND RADIATION COMBINED WITH SURGERY

	Radiation alone			Radiation combined with surgery		
	Number of cases	Five year cures		Number of cases	Five year cures	
		Number	Per cent		Number	Per cent
Adenocarcinoma,* grades I and II	114	45	39.3	67	44	65.7
Adenocarcinoma, grades III and IV	62	14	22.6	45	12	26.6
Adenoacanthoma	19	9	47.4	16	11	68.7
Miscellaneous†	15	4	20.6	4	0	00.0
Total	210	72	33.2	132	67	42.6

*Also includes so-called adenoma malignum cases
†Includes cases in which scanty material or other factors made histologic grading impossible.

TABLE XIV.—SECONDARY CASES
FIVE YEAR END-RESULTS

	Memorial Hospital	Gynecologic Division
Total number of secondary cases	163	146
Indeterminate group Dead as a result of other causes and without recurrence	11	11
Lost track of without recurrence	8	6
Total number of indetermine results	19	17
Determinate group Total number minus those of indeterminate group	144	129
Failures Dead as a result of carcinoma	78	71
Lost track of with disease (probably dead)	5	5
Living with recurrence	8	8
Total number of failures in treatment	91	84
Successful results Free of carcinoma after five years or more	53	45
Five year end-results Successful results divided by determinate group	(53/144) 36.79%	(45/129) 34.88%
Absolute cure rate Successful results divided by total number of cases	(53/163) 32.51%	(45/146) 30.82%

TABLE XV.—SECONDARY CASES
RELATION OF CLINICAL GROUP TO END-RESULTS

	Prophylactic group			Recurrent group		
	No. of cases	Five year cures		No. of cases	Five year cures	
		Number	Per cent		Number	Per cent
Entire Hospital (163 cases)	30	20	66.66	133	33	24.81
Gynecologic Division (146 cases)	25	16	64.00	121	29	23.96

had been surgically treated before being referred to Memorial Hospital, 57, or 66.4 per cent, had received only a supracervical hysterectomy. Thirty-five, or 61.4 per cent, of those women who had had a supracervical amputation of the uterus had histologically verified carcinoma in the cervical stump at the time of their initial examination here. It is obvious that entirely too many women who are suffering from vaginal bleeding are still being treated by a subtotal hysterectomy without curettage or adequate examination of the cervix.

SUMMARY AND CONCLUSIONS

Five hundred and thirty-one histologically verified cases of carcinoma of the corpus uteri were admitted to Memorial Hospital during the period 1926 to 1940, inclusive. The absolute 5 year cure rate on this unsorted group of cases was 38 per cent.

The primary cases of the series numbered 386 of which 39.9 per cent were alive and well at the end of 5 years. By subtracting the patients lost track of when free of cancer and those dying of intercurrent, unrelated illness, the apparent cure rate for 5 years is about 45 per cent.

Of the secondary cases, there were 30 patients who came to the Memorial Hospital without clinical evidence of cancer and of these there were 20 five year cures. The patients admitted to the service with recurrences numbered 133 and, of these, 24.8 per cent were alive and well after 5 years.

The prognosis in carcinoma of the corpus depends on 3 factors: (a) the gross extent of the disease; (b) the histologic type; and (c) the type of therapy employed. Analysis of the present series was made to evaluate these points.

The effect of the gross extent of the disease is shown by the 5 year end-results in 5 specified groups as follows: Group I, uterus not enlarged, 66.6 per cent; Group II A, uterus not larger than a 2½ months' gestation, 54.4 per cent; Group II B, uterus larger than a 2½ months' gestation, 37.9 per cent; Group III A, extension of carcinoma to cervix, 24.3 per cent; Group III B, extension of carcinoma beyond uterus, 11.2 per cent.

The effect of histologic type is shown by the 5 year end-results in 3 classifications as follows: adenocarcinoma, grades I and II, 47.2 per cent; adenocarcinoma, grades III and IV, 22.8 per cent; adenoacanthoma, 51.3 per cent.

The relation of type of treatment to end-results is more difficult to evaluate. In the cases in which hysterectomy was performed a 5 year cure rate of 51.1 per cent was shown, while in the group of patients treated only by radiation the figure was 36.8 per cent. The group with treatment limited only to radiation contained, however, more patients in a relatively advanced stage of the disease.

The question of whether the cure rate from hysterectomy is increased when radiation is given in addition could not be answered on the basis of the analysis of this material.

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THE EXCRETION AND CONCENTRATION OF PENICILLIN AND STREPTOMYCIN IN THE ABNORMAL HUMAN BILIARY TRACT: II. HEPATIC BILE

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IN a previous paper the results of studies of the excretion and concentration of penicillin and streptomycin in the human gall bladder were reported (6). We now wish to present our findings relative to the excretion and concentration of these antibiotic agents in the hepatic bile of the abnormal human biliary tract. The reader is referred to the previous paper for introductory remarks and for a review of the literature.

METHOD OF STUDY

Twenty-three patients, each of whom had undergone exploratory choledochostomy and insertion of a T tube in the common duct, were selected. Sixteen of these were used to study the excretion of penicillin; 15, to study the excretion of streptomycin. Eight patients were tested only for excretion of penicillin; 7 only for excretion of streptomycin; and 8, for both. Therefore, on 8 occasions the results with penicillin could be compared with those for streptomycin.

Within a 3 day period after operation each patient was given a single intramuscular injection of either 15,000 units of penicillin or 100,000 units of streptomycin. When both substances were studied in the same subject, a single injection of each was given separately on the same day. Usually 6 to 8 hours were allowed to elapse before study of the second antibiotic agent was undertaken. Specimens of bile were collected from the T tubes at intervals of one-half hour to 1 hour up to 3 hours after injection of the antibiotic agent. Specimens of blood were obtained at the same time from 4 patients who were given penicillin, and from a similar number given streptomycin. The antibiotic activity of all specimens was determined in the same manner as was done in the previous study (6). Within a 3 week period the study was repeated for penicillin in 5 cases and for streptomycin in 8 cases, in order to determine any change that might have occurred in the ability of the liver to excrete the antibiotic agent.

When the patient was jaundiced at the time of operation, it was noticed whether the jaundice was increasing, stationary or subsiding, as shown by estimations of the serum bilirubin level. In addition, in most cases either an oral hippuric acid test or a sulfobromophthalein hepatic function test was done during the stay in the hospital. The former was performed in the presence of an elevated serum bilirubin level; the latter, in its absence. These observations were made in an attempt to correlate hepatic function tests with the ability of the liver to excrete antibiotic agents. An excretion in the urine of 3 grams of benzoic acid or its equivalent in hippuric acid is a normal value for the hippuric acid test, and retention of dye, "grade 0," in the blood serum is a normal value for the sulfobromophthalein test.

RESULTS

1. *Penicillin.* The results are collected in Tables I and II and are represented in Figures 1 to 3 inclusive. Table I states briefly a few pertinent facts in the history and the essential laboratory studies of the individual patients. Table II indicates the levels of penicillin activity in the bile in the initial study done within the first 3 days after operation. Reference to Figure 1 shows the similarity of the blood levels of the 4 patients studied. It is very likely that, had the other patients been so

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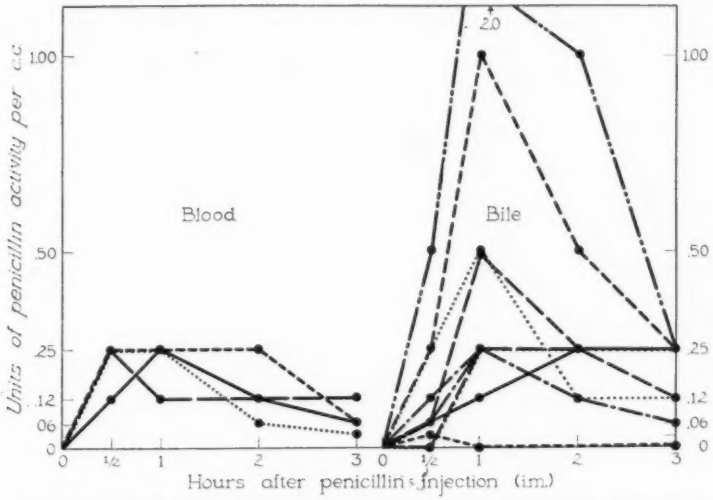

Fig. 1. Levels of penicillin activity in blood serum and hepatic bile after 15,000 units of penicillin had been given intramuscularly. Four patients were used for the blood curves and 16 for the bile curves. Of the latter, 5 failed to excrete penicillin into the bile. The graph demonstrates the similarity of the curves of the levels in blood and dissimilarity of those in bile.

studied, similar curves would have been obtained. On the other hand, a composite graph of the levels in the bile shows great variation in the height and shape of the curves. It is the purpose of this study to determine the factors responsible for this variation. In addition, it is noticed that the levels of activity are higher in the bile than in the blood, indicating that the liver concentrates penicillin.

The patients were divided into three groups, on the basis of their ability to excrete the penicillin on initial study: those who failed to excrete penicillin, those who excreted it in very small amounts, and those who excreted it in high concentration. An arbitrary figure of 0.24 unit per cubic centimeter was decided on to separate those who excrete small from those who excrete large amounts, because in a previous study (6) it was observed that the smallest concentration of penicillin in gall-bladder bile obtained within the first 4 hours after injection was at least 0.24 unit per cubic centimeter. Since all persons but one in that investigation had presumably normal hepatic function, it was assumed that that level was representative of the lowest limit of excretion in a normal subject.

It is realized that the volume of bile excreted during the 3 hour period for each study is not the same for all patients. However, the amounts excreted during 24 hours were usually quite similar, 250 to 350 cubic centimeters. While it is conceivable that if one patient excretes 50 cubic centimeters over the 3 hour period of study, whereas another excretes 20 cubic centimeters, the first patient may dilute any antibiotic agent excreted and mask the results, this was not usually the case. Often the highest levels of penicillin were found among patients excreting relatively large volumes of bile at the time of study, and the lowest levels, among those excreting small amounts of concentrated bile. Generally speaking, however, this factor was of little importance, since most patients excreted similar volumes of bile.

Group 1, no excretion of penicillin: Five patients failed to excrete penicillin within the 3 hour period of observation (Table I). In several cases the observations were repeated the following day with similar results. A short résumé of the history and laboratory findings in these cases follows:

CASE 1. The patient gave a history of recurrent colic in the upper part of the abdomen, often with

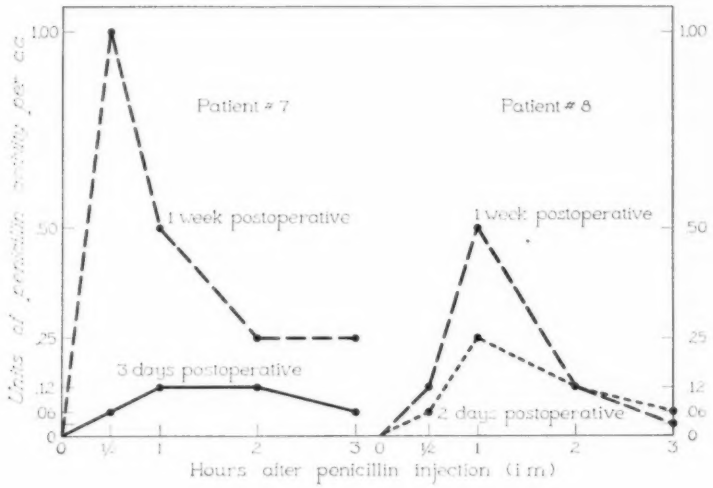

Fig. 2.

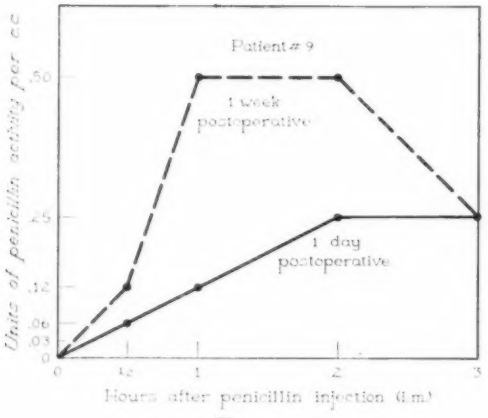

Fig. 3.

Figs. 2 and 3. Effect of relief of biliary obstruction on excretion of penicillin in hepatic bile. Definite increase of excretion 1 week after operation over that 1 to 3 days after operation.

chills and fever, for 1 year. The preoperative laboratory studies gave results within normal limits. He was found at operation to have calculi in the gall bladder and common duct. The gall bladder was removed, and a T tube was inserted in the common duct. Excretion studies for penicillin in hepatic bile were undertaken on the second and fourth days after operation. All specimens were reported as having no penicillin activity. On the third postoperative day, the patient had repeated chills and a spiking temperature reaching more than 102 degrees F. Two cultures of bile from the common duct were reported as positive for Escherichia coli. The serum bilirubin level, which had been normal preoperatively, was reported as 2.75 milligrams per 100 cubic centimeters direct and 0.57 milligram per 100 cubic centimeters indirect. Leucocytes numbered 7,200 in each cubic millimeter of blood and 91 per cent of the leucocytes were neutrophils. The result of the sulfobromophthalein test of hepatic function was reported as retention of dye, grade 2 (12 to 24 per cent). Intramuscular administration of 15,000 units of penicillin every 3 hours was begun. On the eighth postoperative day the temperature returned to normal, the serum bilirubin level fell to 1.5 milligram per 100 cubic centimeters direct and 0.4 milligram per 100 cubic centimeters indirect. The sulfobromophthalein test was reported as showing no retention and the percentage of neutrophils was 70. The T tube stopped draining, and color returned to the stools.

TABLE I.—EXCRETION OF PENICILLIN IN HEPATIC BILE FOLLOWING INTRAMUSCULAR INJECTION OF 15,000 UNITS (SUMMARY OF PERTINENT DATA OF 16 CASES)*

Case	Duration of jaundice	Hepatic function test		Preoperative serum bilirubin, mgm. per 100 c.c.		Maximal excretion of penicillin, units per c.c. of bile		
		Sulfobromophthalein†	Hippuric acid‡	Direct	Indirect	Initial study	First repeat study (days after initial study)	Second repeat study (days after initial study)
1	(No—preop. yes—postop.) (Chills and fever—1 year)	Grade 2 Grade 0 (12 days later)		2.75	0.57	0	0 (2 days later)	0.12 (12 days later)
2	2 mos.		1.26	33.6	1.8	0	0 (1 wk. later)	0 (15 days later)
3	1 mo.		1.79	35.5	2.28	0		
4	3 wks.		2.04	4.0	1.0	0		
5	3 mos.		2.8	69.6	4.2	0		
6	10 mos. (recurrent)			10.6§	2.1§	0.03		
7	Recurrent (fistula)			3.2	0.7	0.12	1.0 (4 days later)‖	
8	1 mo. (recurrent)		3.03	5.1§	1.55§	0.25	0.5 (5 days later)‖	
9	1 yr. (recurrent)		2.01	15.6§	1.8§	0.25	0.5 (1 wk. later)‖	
10	9 days		2.64	2.45§	1.7§	0.25		
11	5 wks.			18.35§	1.9§	0.25		
12	None	Grade 1		0	0.4	0.25‖		
13	None	Grade 0		0	0.8	0.5‖		
14	None	Grade 0	3.84	0	0.8	0.5‖		
15	None	Grade 0		0	0.4	1.0‖		
16	7 days (first attack)		2.8	8.1§	1.0§	2.0‖		

*The amount of bile excreted during 24 hours varied between 250 and 350 c.c. for all cases.
†Reported as degree of retention (grades 1–4).
‡Reported here as grams of benzoic acid excreted on oral hippuric acid test (normal, 3 gm.).
§Level of bilirubin falling when study was made.
‖Normal serum bilirubin when study was made.

On the twelfth day, with the T tube still in place, another attempt to study excretion of penicillin was made. This time a single small specimen of bile was obtained 1½ hours after injection of penicillin and was reported as containing 0.12 unit of penicillin per cubic centimeter. Bile for culture of bacteria was collected under conditions too difficult to be useful.

This, no doubt, was a case in which Escherichia coli cholangitis responded to drainage. That the penicillin was a factor in helping to overcome the process is doubtful, since penicillin is known to be very inactive against Escherichia coli, and since early in the postoperative course none of the antibiotic agent was excreted into the bile duct. It appears that simple mechanical drainage was the effective agent here, an observation frequently made in the past.

CASE 2. The patient had undergone a cholecystectomy 1 year before she came to the clinic. Ten months later persistent jaundice, pain in the upper part of the abdomen, and recurrent chills and fever had developed. The significant laboratory work showed a serum bilirubin level of 33.6 milligrams per 100 cubic centimeters direct and 1.8 milligrams per 100 cubic centimeters indirect. Hepaticostomy was performed, and a large catheter was left in place. "White bile" drained for many days. After parenteral administration of penicillin, no penicillin activity was obtained in specimens of bile removed either the day after operation or on the eighth and fifteenth days, in spite of the fact that the bile had acquired a green color by that time. The direct serum bilirubin level remained greater than 30 milligrams per 100 cubic centimeters on dismissal of the patient. She no longer had chills or fever. An oral hippuric acid test of hepatic function performed on the twelfth postoperative day showed impairment, only 1.86 grams of hippuric acid (equivalent to 1.26 gm. of benzoic acid) being excreted in the urine.

In this case the administration of an antibiotic agent in an attempt to help clear up the associated cholangitis might have been credited with the symptomatic improvement which occurred. However, the inability of the liver to excrete penicillin shows how futile the use of penicillin for this purpose would have been. As in Case 1, the improvement of the general and local condition of the patient was due entirely to mechanical drainage.

TABLE II.—EXCRETION OF PENICILLIN IN HEPATIC BILE FOLLOWING INTRAMUSCULAR INJECTION OF 100,000 UNITS (SUMMARY OF LEVELS ON INITIAL STUDY)

Group	Case	Penicillin level, units per c.c. of bile			
		½ hr.	1 hr.	2 hrs.	3 hrs.
1	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
2	6	0	0.03	0	0
	7	0.06	0.12	0.12	0.06
3	8	0.06	0.25	0.12	0.06
	9	0.06	0.12	0.25	0.25
	10	0	0.25	0.25	0.12
	11	0.12	0.25	0.12	0.06
	12	0	0.25	0.25	0.25
	13	0.25	0.5	0.12	0.12
	14	0.06	0.5	0.25	0.12
	15	0.25	1.0	0.5	0.25
	16	0.5	2.0	1.0	0.25

CASE 3. The patient had undergone cholecystectomy previously. For 1 month he had continuous jaundice and acholic stools, but no chills, fever, or pain. Exploratory choledochostomy was performed. No obstruction was found, and it was the surgeon's impression that the patient had intrahepatic jaundice. The preoperative serum bilirubin levels varied from 29.1 milligrams per 100 cubic centimeters to 35.5 milligrams per 100 cubic centimeters direct, and from 1.8 milligrams per 100 cubic centimeters to 2.28 milligrams per 100 cubic centimeters indirect. A preoperative hippuric acid excretion test showed severe impairment of hepatic function, since only 2.63 grams of hippuric acid (or 1.79 gm. of benzoic acid) was excreted in the urine. On the fourth postoperative day there was no excretion of penicillin in specimens of bile collected over hourly periods. Postoperatively, the serum bilirubin levels remained high, and the patient was dismissed from the clinic with his T tube in place.

CASE 4. The patient had had recurrent colic in the right upper quadrant of the abdomen for 1 year and had been icteric for 3 weeks. The serum bilirubin level was 4 milligrams per 100 cubic centimeters direct and 1 milligram per 100 cubic centimeters indirect. Following an oral hippuric acid test of hepatic function, it was reported that only 2.04 grams of benzoic acid had been excreted in the urine (normal, 3 gm.). Two cultures of bile from the common duct were reported as positive for Escherichia coli. No penicillin was excreted in the bile on the fourth postoperative day. The patient's jaundice cleared rapidly and he had no immediate postoperative difficulty.

CASE 5. The patient was admitted with a history of intense jaundice for several months. The serum bilirubin level was 69.6 milligrams per 100 cubic centimeters direct and 4.2 milligrams per 100 cubic centimeters indirect. The oral hippuric acid test of hepatic function was reported as giving normal results. At operation a carcinoma of the gall bladder with a local metastatic growth obstructing the common duct was found. The duct was opened, "white bile" was obtained, and a T tube was inserted. On the fifth postoperative day there was no excretion of penicillin into the bile. The patient was dismissed unimproved on the eleventh postoperative day.

It is interesting to observe that in 4 of the 5 cases there was persistent jaundice before operation and in 2 of these cases "white bile" was obtained from the bile ducts at operation. However, even when color returned to the bile in 1 of the cases, indicating that some of the function of the liver was returning, penicillin was still not excreted in the bile. In 4 of the 5 cases there was impairment of hepatic function as shown by the usual tests of hepatic function. In 1 case, in which the patient was not icteric preoperatively, jaundice, chills, and fever developed soon after operation. During this time no penicillin was excreted, but as the cholangitis cleared, parenterally given penicillin was recovered in the bile.

Group 2, excretion of small amounts of penicillin:

CASE 6. The patient had had intermittent chills and fever for 3 months and intermittent jaundice for 10 months. The serum bilirubin level on admission was 10.6 milligrams per 100 cubic centimeters direct, and 2.1 milligrams per 100 cubic centimeters indirect. Operation was performed 10 days later, when the jaundice was definitely subsiding. Cholecystectomy and choledocholithotomy were performed and a T tube was left in place. On the third postoperative day penicillin that had been administered parenterally was excreted in a concentration of 0.03 unit per cubic centimeter of bile in the 1 hour specimen, but all the other specimens up to 3 hours showed no activity.

CASE 7. The patient had had a biliary fistula since cholecystectomy had been performed 4 months before. The serum bilirubin level varied from 2.6 milligrams per 100 cubic centimeters to 3.2 milligrams per 100 cubic centimeters direct. A stone was removed from the common duct and a T tube was inserted. On the second postoperative day, all specimens of bile collected up to 3 hours showed a maximal penicillin level of 0.12 unit per cubic centimeter after parenteral administration of penicillin.

TABLE III.—EXCRETION OF STREPTOMYCIN IN HEPATIC BILE FOLLOWING INTRAMUSCULAR INJECTION OF 100,000 UNITS (SUMMARY OF PERTINENT DATA OF 15 CASES)*

Case	Duration of jaundice	Hepatic function test		Preoperative serum bilirubin, mgm. per 100 c.c.		Maximal excretion of streptomycin, units per c.c. of bile		
		Sulfobromophthalein†	Hippuric acid‡	Direct	Indirect	Initial study	First repeat study	Second repeat study
2	2 mos.		1.26	33.6	1.8	0	0 (1 wk. later)	0 (15 days later)
17	3 mos.		2.20	1.55	2.5	0		
18	Recurrent (fistula)	Grade 0	3.53	8.9§	0.9§	0	0 (3 wks. later)	
19	?		1.08	9.1	1.6	0.7		
20	3 wks.		3.96	5.1§	3.4§	0.6	1.12(3 wks.later)	
7	Recurrent (fistula)			3.2	0.7	1.14	2.25(6 days later)‖	
12	None	Grade 1		0	0.4	1.39‖		
14	None	Grade 0	3.84	0	0.8	1.5‖		
23	None	Grade 0	2.6	2.7§	1.2§	1.05	1.5(4 days later)‖	1.9(3 wks. later)‖
10	9 days		2.64	2.45§	1.7§	1.5		
22	Recurrent (fistula)		2.45	1.9§	0.6§	1.58‖	2.79 (6 days later) ‖	
9	1 yr. (recurrent)		2.01	15.6§	1.8§	1.81‖	1.8(5 days later)‖	
8	1 mo. (recurrent)		3.03	5.1§	1.55§	2.0‖	2.4(5 days later)‖	
21	3 wks.		3.11	10.2§	1.1§	2.53‖		
16	7 days (first attack)		2.8	8.1§	1.0§	3.8‖		

*The amount of bile excreted in 24 hours varied from 250 to 350 c.c. for all cases.
†Reported as degree of retention (grades 1–4).
‡Reported here as grams of benzoic acid excreted on oral hippuric acid test (normal, 3 gm.).
§Level of serum bilirubin falling when study was made.
‖Normal serum bilirubin when study was made.

In both of these cases there was a history of chronic icterus and recurrent episodes of cholangitis. Both patients were apparently recovering from acute obstructive episodes when the study was made.

Group 3, excretion of large amounts of penicillin: The remaining 9 patients excreted penicillin in a concentration of at least 0.25 unit per cubic centimeter of bile. Five of these had no previous history of jaundice and in 4 of the 5 cases the maximal concentration of penicillin in bile varied from 0.5 unit per cubic centimeter to 2 units per cubic centimeter (Cases 13 to 16, inclusive). In the one nonicteric case (Case 12) in which the level did not exceed 0.25 unit per cubic centimeter it was persistent at this concentration in all except the half hour specimen. The remaining 4 patients (Cases 8 to 11 inclusive) gave a history of rather recent onset of jaundice and, at the time of study, they gave evidence of subsiding icterus. Two of these showed impairment of excretion of hippuric acid.

In general the highest levels of excretion of penicillin were found among those patients who had no history of recent or past jaundice, and who exhibited good hepatic function, as shown by the tests employed. With a history of persistent jaundice, and with impairment of hepatic function, less penicillin was excreted, until in 5 cases none was excreted in the bile.

Excretion studies were repeated a week after the initial tests in 5 cases (Table I). Two of these have been described in detail in the previous paragraphs (Cases 1 and 2). It was seen in Case 1 that after 12 days of T tube drainage, penicillin was excreted in a concentration of 0.12 unit per cubic centimeter, where initially there was no excretion. After 2 weeks the patient in Case 2 was still unable to excrete penicillin. The 3 other patients followed showed a definite increase in ability of the liver to excrete penicillin (Cases 7, 8, and 9), as indicated in Figures 2 and 3. One of these patients (Case 7), who had an excretion level of 0.12 unit per cubic centimeter initially,

TABLE IV.—EXCRETION OF STREPTOMYCIN IN HEPATIC BILE FOLLOWING INTRAMUSCULAR INJECTION OF 100,000 UNITS (SUMMARY OF LEVELS ON INITIAL STUDY)

Group	Case	Streptomycin level, units per c.c. of bile			
		½ hr.	1 hr.	2 hrs.	3 hrs.
1	2	0	0	0	0
	17	0	0	0	0
	18	0	0	0	0
2	19	0	0.25	0.7	<0.25
	20	0	0	0.6	0.6
3	7	0	<0.5	1.14	0.85
	12	0	Slight	1.3	1.39
	14	0	1.5	1	1.2
	23	0	0	1.05	0.95
	10	1	1.15	1.5	1.4
	22	Trace	1.0	1.4	1.58
	9	1.0	1.18	1.81	1.13
	8	0.5	1.35	2.0	1.2
	21	0	1.64	2.58	2.44
	16	Trace	2.7	3.8	0.95

showed an increase to 1 unit per cubic centimeter in the half hour specimen. The patient in Case 8 excreted 0.25 unit per cubic centimeter soon after operation, and 0.5 unit per cubic centimeter 5 days later. This was a patient who had recurrent jaundice of 1 month's duration and good hepatic function, as shown by the oral hippuric acid excretion test. The patient in Case 9 excreted 0.25 unit per cubic centimeter at first, and 0.5 unit per cubic centimeter later.

Consequently, it is noted that in 4 of the 5 patients followed there was a definite increase in the ability of the liver to excrete penicillin after a variable period of T tube drainage. Also, from this it would appear that the lower limit of excretion, 0.25 unit per cubic centimeter, is an index of impaired excretion, since in all 3 cases in which hepatic function was not seriously impaired, a level of at least 0.5 unit per cubic centimeter was obtained on the second determination after a week of drainage. While this group is small, the results are suggestive. In addition, these results support a previous finding that the patients without jaundice or hepatic damage excreted at least 0.5 unit per cubic centimeter on the first determination soon after operation (Cases 13 to 16 inclusive), as well as the finding that in all cases in which the cystic duct was patent the level after 45 minutes was at least 0.5 unit per cubic centimeter, in spite of possible dilution in the gall bladder (6).

2. Streptomycin. The results are collected in Tables III and IV and are represented in Figures 4 to 7, inclusive. Table III states briefly a few facts in the history and essential laboratory findings. Table IV indicates the levels of streptomycin activity in the bile on initial study done soon after operation. Reference to Figure 4 demonstrates the constancy of the height and persistence of the curves of streptomycin activity in the blood serum of each of the 4 patients so studied. A similar curve might be expected in all the other subjects, were blood serum levels determined for them. As was true with penicillin, however, the streptomycin levels in hepatic bile varied in most of these cases. In addition, the levels of activity in the bile were generally less than in the blood, suggesting that the liver did not concentrate streptomycin.

Here, too, it is well to divide the patients into 3 groups, according to their ability to excrete streptomycin in the bile on initial study soon after operation. An arbitrary figure of 1 unit per cubic centimeter of bile was chosen to separate those who excreted small from those who excreted large amounts. This figure corresponds to 0.24 unit per cubic centimeter of bile chosen for penicillin, and was arrived at in the same manner (see the section on penicillin).

Group 1, no excretion of streptomycin: Three patients failed to excrete streptomycin in the bile during the 3 hour period observed. One of these has been described previously in detail in the section on excretion of penicillin (Case 2). A brief history of the other 2 patients follows:

CASE 17. The patient had a history of dark urine, light stools, and jaundice for 3 months. A serum bilirubin level a week before operation was 1.55 milligrams per 100 cubic centimeters direct and 2.5 milligrams per 100 cubic centimeters indirect. The hippuric acid test of hepatic function showed definite impairment. At operation cholecystectomy and choledocholithotomy were performed, and a T tube

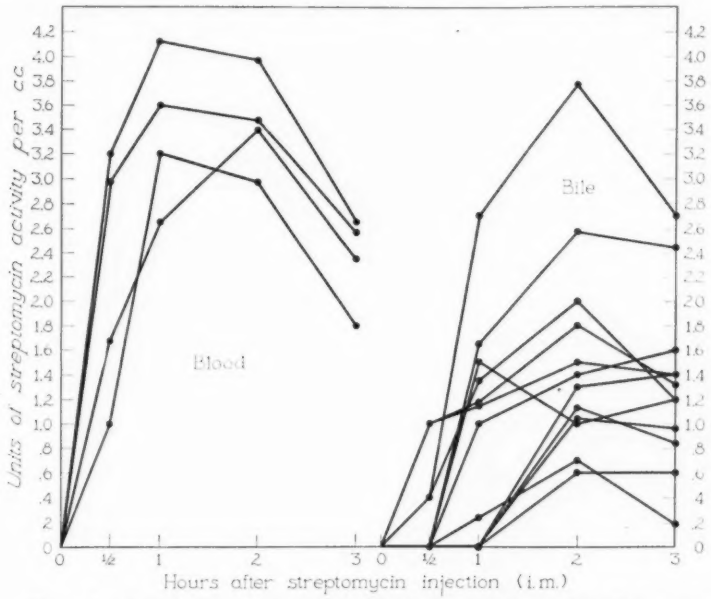

Fig. 4. Levels of streptomycin activity in blood serum and hepatic bile after 100,000 units of streptomycin had been given intramuscularly. Four patients were used for the blood curves and 15 for the bile curves. Of the latter, 3 failed to excrete streptomycin in the bile. The graph demonstrates the similarity of the curves of the levels in blood and dissimilarity of those in bile.

was inserted. Two days after operation, no streptomycin was excreted in the bile. This patient was not studied further.

CASE 18. A biliary fistula developed following cholecystectomy done 3 months before the patient came to the clinic. On several occasions when the fistula became obstructed, she had chills, fever, and jaundice. On admission her serum bilirubin level was 8.9 milligrams per 100 cubic centimeters direct and 0.9 milligram per 100 cubic centimeters indirect. Several days later the common duct was reconstructed over a T tube. Studies of excretion of streptomycin on the third postoperative day showed no excretion in the bile, in spite of the fact that the serum bilirubin level was almost normal, and the hippuric acid test of hepatic function gave definitely normal results. All studies were repeated 3 weeks later, with the same results.

Group 2, excretion of small amounts of streptomycin: Two patients excreted a maximal concentration of less than 1 unit per cubic centimeter of bile.

CASE 19. Operation was performed because of chronic dyspepsia, with recurrent bouts of colic in the right upper quadrant of the abdomen for several years. A functioning gall bladder with stones was found on roentgenographic examination. At operation greatly dilated common and cystic ducts were found, and the liver was reported as showing "hepatitis, grade 1+." Cholecystectomy and choledochostomy were performed. The following day a streptomycin excretion study was made. The maximal level attained was 0.7 unit per cubic centimeter in the 1½ hour specimen. A serum bilirubin level the following day was 9.1 milligrams per 100 cubic centimeters direct and 1.6 milligrams per 100 cubic centimeters indirect. A hippuric acid test of hepatic function done 2 days later showed severe impairment. It was impossible to repeat the streptomycin excretion study, since little material was obtainable from the T tube after the fourth day. However, on the ninth postoperative day the serum bilirubin level was 3.6 milligrams per 100 cubic centimeters direct and 0.8 milligram per 100 cubic centimeters indirect.

CASE 20. Cholecystectomy and choledochostomy had been performed in 1943. The patient was well until 2 weeks before his present admission when pain in the right upper quadrant of the abdomen, fever, dark urine, and jaundice developed. The serum bilirubin level 4 days before operation was 5.1 milligrams per 100 cubic centimeters direct and 3.4 milligrams per 100 cubic centimeters indirect. The hippuric acid liver function test gave normal results. Choledocholithotomy and choledochostomy were performed. On the second postoperative day the pa-

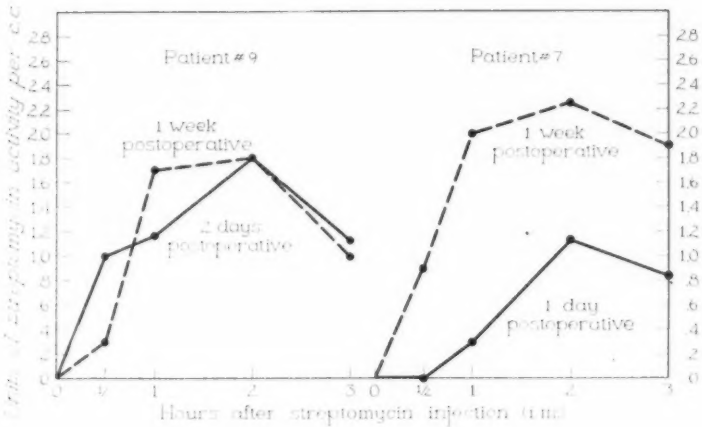

Fig. 5.

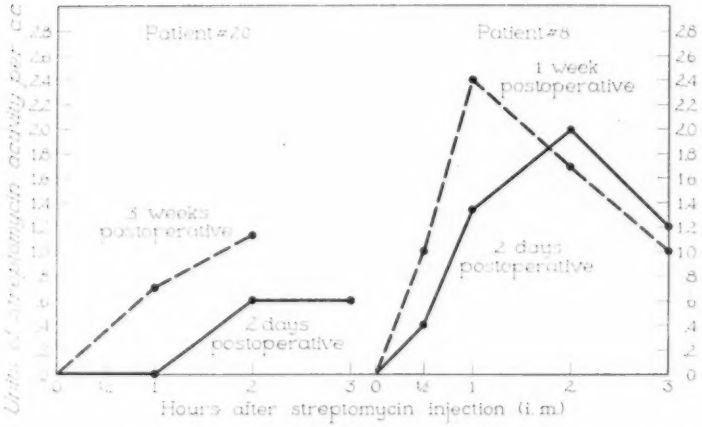

Fig. 6.

Figs. 5, 6, and 7. Effect of relief of biliary obstruction on streptomycin excretion in hepatic bile. Definite increase of excretion 1 to 3 weeks after operation over that 1 to 3 days after operation.

tient failed to excrete more than 0.6 unit of streptomycin per cubic centimeter of bile. However, when the study was repeated 3 weeks later, at which time his serum bilirubin level was 2.4 milligrams per 100 cubic centimeters direct and 0.9 milligram per 100 cubic centimeters indirect, the streptomycin activity of the 1¾ hour specimen of bile was 1.12 units per cubic centimeter.

In résumé, one patient (Case 2) failed to excrete either streptomycin or penicillin in separate studies. This fact suggests that the excretion of these antibiotic agents is subject to the same factor of adequate hepatic function. As with penicillin, 2 of the 3 patients who failed to excrete streptomycin in the bile had a history of persistent jaundice before operation and both showed impairment of response in the hippuric acid excretion test. The results found in the third patient (Case 18) are somewhat difficult to explain. Although her hippuric acid excretion test and sulfobromophthalein hepatic function test gave normal results, she failed to excrete streptomycin on 2 occasions, 3 weeks apart. The results of the first study done soon after operation might be ex-

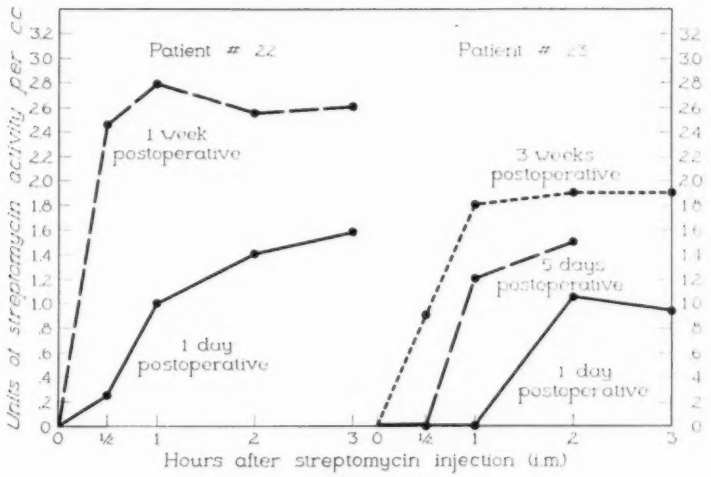

Fig. 7.

plained on the basis of a recent episode of obstructive jaundice which had temporarily impaired some of the hepatic functions (such as streptomycin excretion). However, after 3 weeks, when her jaundice had completely subsided, it was expected that she would excrete streptomycin. It would appear that the excretion of streptomycin is a hepatic function quite apart from all the others, since it is well known that many hepatic functions may be normal, while others are definitely impaired.

Of the 2 patients who excreted small amounts of streptomycin in the bile, one had definite hepatitis, as shown by the surgeon's operative note, corroborated by a definitely impaired hippuric acid excretion test. The other patient was studied soon after the onset of an episode of obstructive jaundice due to a stone in the common duct. The serum bilirubin was elevated at this time. However, in a repetition of the study 3 weeks later, when jaundice had subsided, he excreted a concentration of streptomycin twice that found on primary investigation. This was in the presence of good hepatic function, as shown by the hippuric acid excretion test.

Group 3, excretion of large amounts of streptomycin: Ten patients excreted more than 1 unit per cubic centimeter on initial study. In 2 cases the serum bilirubin levels were normal at the time of examination. In the other 8 cases the jaundice was definitely subsiding. The level of streptomycin activity in all of these cases varied from 1.05 units per cubic centimeter to 3.8 units per cubic centimeter.

As with penicillin, the highest levels of streptomycin activity were among those patients who had no history of jaundice and who had normal hepatic function. With persistent jaundice and impairment of hepatic function streptomycin was excreted in lesser amounts, until in 3 cases none was excreted.

In all cases but one, where the hippuric acid excretion test gave normal results, and where no jaundice was present at the time of study, the excretion level was more than 2 units per cubic centimeter. However, in the one exception, a healthy robust man with no previous history of jaundice and with good hepatic function excreted only 1.5 units per cubic centimeter. This, then, must be considered a normal level.

After a lapse of 1 to 3 weeks the excretion studies were repeated for 8 patients (Table III). Two of these failed to excrete streptomycin, even after a period of prolonged drainage (Cases 2 and 18). They have both been described fully elsewhere. In all the other cases there was a definite increase of excretion, so that in several the level in the bile was doubled (Cases 7, 8, 9, 20, 22, and 23). After a

period of T tube drainage, regardless of the primary condition, the minimal excretion level in those tested was 1.8 units per cubic centimeter, compared to 1.05 units per cubic centimeter on initial examination. It would appear, then, that the lower limit of excretion chosen as normal; namely, 1 unit per cubic centimeter, is an index of some impairment of ability to excrete streptomycin, since in all cases in which the studies were repeated later, a higher level of excretion, 1.8 units or more per cubic centimeter, was found. In 3 weeks the patient in Case 20 doubled his ability to excrete streptomycin and although the level was only 1.12 units per cubic centimeter, it is quite possible that, were the studies repeated again, the level would have been higher. Further repetition of the studies was not practicable in this case, since the T tube was removed several days later.

In 8 cases studies were carried out with both penicillin and streptomycin (Cases 2, 7, 8, 9, 10, 12, 14, and 16). Reference to Tables I and III demonstrates how both substances are excreted quite similarly by the same patients. As mentioned previously, 1 patient (Case 2) failed to excrete either penicillin or streptomycin. When a large amount of one was excreted, a large amount of the other was usually also excreted. In 3 cases studies were repeated at a later date. In all cases there was an increase in the excretion of both antibiotic agents, and to a similar degree. This small series indicates the similarity of their excretion in hepatic bile.

COMMENT

In general, the concentration of an antibiotic agent excreted in the hepatic bile is roughly inversely proportional to the degree of hepatic damage. In any case of obstructive jaundice, as the obstruction persists, more and more evidence of hepatic damage appears. The ability to excrete penicillin or streptomycin seems to be a rather sensitive index of hepatic damage. Early in the course of one case of cholangitis (Case 1) no penicillin was excreted but, as soon as the symptoms and signs of infection subsided, penicillin was excreted into the bile. In all cases of long, persistent obstructive jaundice no antibiotic agent was excreted. In less prolonged obstruction there was some excretion. However, in all cases but one in which excretion studies were repeated after one or more weeks of mechanical drainage with relief of obstruction, penicillin was present in greater amounts than initially. The significance of this is obvious. It has long been recognized that the condition of patients who have cholangitis of greater or lesser degree improves with mechanical drainage. Hepatic function returns to normal, and very often the cholangitis is overcome. As is true with other regions of enclosed infection, surgical drainage is necessary to institute resolution and repair.

As a result of this study it appears that a minimal level of 0.5 unit of penicillin activity per cubic centimeter of bile within a 3 hour period after an intramuscular injection of 15,000 units of penicillin is indicative of a relatively normal liver. The same is true for a level of 1.5 units of streptomycin per cubic centimeter of bile after an intramuscular injection of 100,000 units of streptomycin. Levels less than these suggest some impairment of hepatic function. The facts supporting this conclusion are, first, that the few normal patients studied excreted at least those levels; second, that all patients who excreted less than these levels initially were able to excrete at least these levels 1 or more weeks later.

One patient had intrahepatic jaundice. He was unable to excrete penicillin. In view of our previous observations, this was not surprising. In intrahepatic jaundice, hepatic cellular damage and obstruction of the biliary canaliculi resulting from degenerative processes in the hepatic cells are present. This combination appears to prevent penicillin from entering the extrahepatic bile ducts.

The clinical application of these findings is worthy of consideration. In many cases cholangitis is treated conservatively. All the agents which might combat the infecting organisms are employed. Until recently the sulfonamides were administered with the hope that they might prove useful. No references to the excretion of these drugs into the bile in cases of cholangitis were found. The few reports of cases in the literature are rather contradictory

and are usually based on clinical observation (1–5). It is known that in many cases cholangitis goes into long periods of quiescence in the absence of any active treatment. The cures attributed to the sulfonamides under these circumstances are open to question, particularly in view of the findings in the present study. While it cannot be said that the sulfonamides are excreted into the bile in the same manner as are the antibiotic agents, the few reports available suggest that they do behave similarly.

Generally speaking, in the presence of definite cholangitis, whenever possible, it is considered good treatment to institute drainage. While at times this may be medical, more often it is surgical. This is so because such cases are usually associated with obstruction in the biliary tract. It is the usual surgical experience that in these cases the response to such measures is good.

While obstruction to the biliary tract is still present, the antibiotic agents do not appear to get into the bile. In addition, the antibiotic agents, in greater or lesser amounts, were excreted in the bile in all cases in which the jaundice was subsiding, and as the serum bilirubin levels returned to normal, the antibiotic levels in the bile increased.

Infection in the hepatic parenchyma itself presents still another problem. In normal dogs it has been shown that there is a high concentration of penicillin in the liver after parenteral administration of penicillin. Whether this is the case in the obstructed and infected liver is open to question. While an antibiotic agent will reach the hepatic cells through the blood stream, its ability actually to enter or bathe the diseased cell is as yet unknown. That it will keep a localized infection in one part of the liver from spreading to other regions in the parenchyma is very likely. That it will keep an infection still localized in the extrahepatic bile ducts from spreading up to the hepatic cells is also possible. Unfortunately, the clinician usually sees the patient who has cholangitis when the process has already invaded the liver itself. However, in the absence of evidence to the contrary, in cases of cholangitis, administration of antibacterial agents would seem indicated in order to protect the liver itself, with the hope that the infection had not yet reached the intrahepatic canaliculi.

The problem of ridding the biliary tree of an infecting organism is not as hopeless as may appear from some of the foregoing remarks. Any patient who has a history of recurrent cholangitis should first be rid of the contributing factor, if it is at all possible. This will include removal of stones, repair of strictures or an attempt to sidetrack the food stream in biliary-intestinal anastomoses. When this is done, it may be expected that the antibiotic agents will get into the biliary tree. If the responsible organism is known, the appropriate antibacterial agent may be given. Within a reasonable period the infection should be overcome. While it may be possible to overcome the organism in a case of recurrent obstructive cholangitis during a period when the inflammation has subsided (for antibiotic agents often do get into the bile in effective concentration), the process is apt to repeat itself unless the etiologic mechanical factor is removed.

CONCLUSIONS

1. After the intramuscular injection of 15,000 units of penicillin or 100,000 units of streptomycin:

a. The antibiotic agent is excreted in high concentration in the hepatic bile of normal patients.

b. A minimal level of 0.5 unit per cubic centimeter for penicillin activity or 1.5 units per cubic centimeter for streptomycin activity in hepatic bile within 3 hours is indicative of a normal liver. Lower levels suggest impairment of excretion.

c. The level of penicillin activity in the bile exceeds that in the blood within the first 3 hours, indicating that the liver concentrates this antibiotic agent.

d. The level of streptomycin activity in the bile is less than that in the blood within the first 3 hours, indicating that the liver does not concentrate this antibiotic agent.

2. In the presence of obstructive jaundice the ability of the liver to excrete the antibiotic agent is impaired.

3. The greater the degree of hepatic damage, the less is the amount of antibiotic agent present in the hepatic bile.

4. In the presence of long-persistent obstructive jaundice, no antibiotic agent is excreted in the bile.

5. As the level of serum bilirubin falls following relief of obstruction of the common duct, more and more of an antibiotic agent is excreted in the bile.

6. Penicillin and streptomycin will probably not be useful in treatment of acute or chronic obstructive cholangitis.

7. The etiologic mechanical factor should be removed in all cases of obstructive jaundice with cholangitis before streptomycin or penicillin can be expected to overcome the infecting organism.

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THE EFFECT OF RADIATION ON VAGINAL CELLS IN CERVICAL CARCINOMA

1. Description of Cellular Changes

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THE effect of roentgen rays on carcinoma of the cervix has long been of great interest to both radiologists and gynecologists. Since most cervical carcinomas are treated by irradiation, any additional knowledge either concerning the radiosensitivity of cervical tumors or the ultimate prognosis would be of value. Any advance in the treatment of this disease by roentgen therapy will depend on further knowledge of the effect and the efficacy of the treatment as it is used at the present time.

The vaginal smear method presents an unique opportunity to study the effects of radiation on cervical malignancy. The vaginal smear is obtained with such ease by merely taking a sample of the vaginal secretion that a patient may be followed as often or as long as desired. The method has the further advantage that a representative group of all the cells, both normal and malignant, of the vaginal and cervical mucosa are seen, not a limited portion as in serial biopsies. We have attempted to determine the effects of x-ray and radium on cervical carcinoma by means of the vaginal smear. We are stating here only the effect of radiation on individual cells. The possible prognostic significance of the method will be discussed in a subsequent publication.

In 1921 Frankle and Amreich studied a series of cases of carcinoma of the cervix by means of biopsies during treatment with radiation. They describe marked swelling of the cells during x-ray and radium treatment. Vacuolization of the malignant cells was also seen as a distinct part of the response to x-ray treatment (2).

From the Vincent Memorial Laboratory of the Vincent Memorial Hospital (the Gynecological Service of the Massachusetts General Hospital).

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Dustin, in 1927, studied 7 cases of epidermoid carcinoma in radiated patients by means of serial biopsies. He has divided the changes seen into four phases. The first phase is that of pyknosis of the nuclei and a decrease in the number of mitoses. The second phase is an increase in the number of atypical mitoses. The third phase represents such an increase in atypical mitoses that no normal mitotic figures were seen. The fourth phase he calls a rise in normal division of cells.

In 1930 Meigs and Parker (6) reported on 5 cases of epidermoid carcinoma on which daily biopsies were done during treatment. The number of both normal and abnormal mitoses was determined. They mention the increase of atypical mitoses on the fourth day after radium treatment and the eventual disappearance of atypical division.

Frola, in 1933, reported 47 cases of cervical carcinoma studied by means of serial biopsy during treatment. Forty-four cases were of epidermoid carcinoma and 3 of adenocarcinoma. He described the atypical mitoses as increasing and then disappearing. The complete disappearance of the malignant cells took place from the eleventh to the fortieth day of treatment. Pyknosis of the nuclei was a prominent feature of the reaction. Degeneration was variable. The sclerosis of blood vessels showed great variation. The connective tissue was infiltrated with polymorphonuclear leucocytes, lymphocytes and occasionally plasma cells. Almost half of the cases showed foreign body giant cell reaction at the termination of treatment. He speaks of a "maturation evolutive" in which the undifferentiated malignant cells mature to become large cells whose nuclei show a sharp nuclear border and are poor in chromatin. There is keratinization and hyalinization of the cells with formation of pearls. Frola also em-

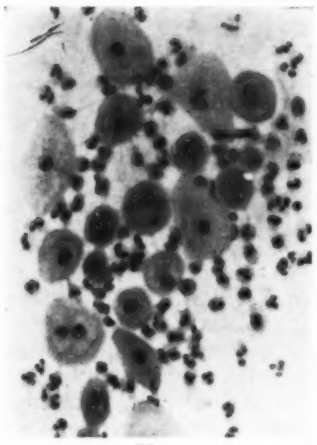

Fig. 1.

Fig. 1. Group of normal basal cells, showing variation in size of cells, but little variation in size of nucleus.

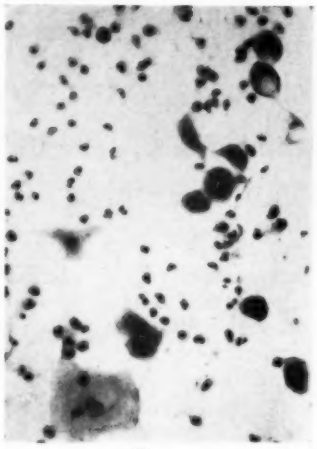

Fig. 2.

Fig. 2. Signet ring type of basal cell in upper right.

Fig. 3.

Fig. 3. Normal precornified and cornified cells.

phasizes the metaplasia of the cells lining the cervical mucous glands during radiation.

In 1935 Arneson and Stewart described the response of tumor to irradiation as swelling of the tumor cells, ballooning degeneration or pyknotic degeneration and fragmentation of the nuclei, progressive cytoplasmic opacity and acidophilia, a tendency to cornification, and finally necrosis and leucocytic infiltration often followed by foreign body giant cell reaction.

MATERIAL

The material for this study comes from three sources: the Tumor Clinic of the Massachusetts General Hospital, the private practice of Dr. J. V. Meigs, and the Pondville Hospital of the Massachusetts State Department of Public Health. We are reporting 206 cases of cervical carcinoma treated by x-ray or radium or both and studied by means of vaginal smear. The cases include patients recently treated and followed during treatment and also those who had treatment from 6 months to 15 years before the first vaginal smear was taken. The group is divided pathologically into 27 cases of adenocarcinoma and 179 cases of epidermoid carcinoma. The majority of the epidermoid carcinomas are classified as grade III, although the study includes cases from all 4 grades.

The radiation in these cases necessarily varies since the group includes patients treated over the past 15 years, and both the amount of x-ray and radium given and the method of administering the dose has changed considerably during this length of time. Most of the patients were considered to have had full therapeutic doses except for a small number who were given palliative therapy. In the recent cases with rare exceptions the patients have been treated with the 1200 kilovolt x-ray machine.

The effect of radiation on the cells of the cervical and vaginal mucosa in patients with carcinoma of the cervix is striking. However, to appreciate fully the changes seen in the vaginal smear it is necessary to have a working knowledge of the cytology of the normal vaginal smear and also the cytology of the malignant cells as seen in the vaginal secretion. It will be helpful perhaps to describe again the cells of the normal vaginal smear. For a more detailed description the reader is referred to the monograph of Papanicolaou and Traut and to our previous publications (7, 8).

The basal cells come from the deepest layer of the vaginal mucosa. They vary in size depending on their position in the basal layer. The inner layer basals are small round cells,

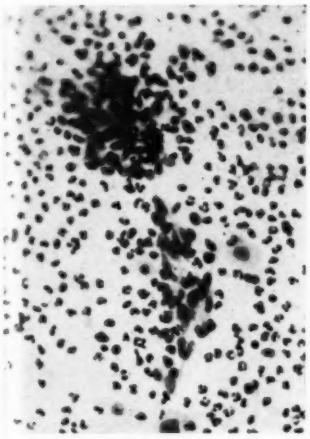

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4. Two groups of small histiocytes showing irregularity in shape of nucleus.

Fig. 5. A foreign body giant cell showing peripheral arrangement of nuclei.

Fig. 6. A group of 4 undifferentiated malignant cells of epidermoid carcinoma of the cervix.

staining deeply basophilic with large active nuclei. The outer layer basals are larger cells having a nucleus similar to that of the inner layer basal cell. Their size increase is due to an increase in cytoplasm rather than nucleus (Fig. 1). The basophilic cytoplasm of the outer layer basal is not so deeply staining and is more transparent. The basal cells are vacuolated occasionally but the vacuoles are usually quite small and quite evenly distributed, or as in the case of the cervical basal cells there is one large vacuole with the nucleus pushed to one side—the signet ring type of cell (Fig. 2). It is important to emphasize that the nuclei of these vacuolated cells of the basal series appear normal in both size and appearance.

The next layer of the vaginal mucosa is composed of precornified cells. This layer is intermediate between the basal layer and the superficial vaginal epithelium. These cells have abundant lightly staining, basophilic, transparent cytoplasm. The cytoplasmic nuclear ratio is greatly increased in comparison to that of the basal cells. The cytoplasm may be wrinkled, or granulated, and the cell borders are often irregular due to the folding over of the cytoplasm (Fig. 3). The nucleus is small and smoothly granular in appearance. The cells of this type are very rarely if ever vacuolated.

The superficial layer of the vaginal mucosa is composed of cornified cells. These cells are similar to the precornified, except for two distinct differences, i.e. the nucleus is small and pyknotic and the cytoplasm is acidophilic (Fig. 3). The same statements concerning wrinkling, folding, and granulation of the cytoplasm apply to these cells of the superficial layer.

Leucocytes are seen very often in the vaginal secretion. In positive smears they are apt to be more numerous than in normal smears. The clumping of leucocytes in tight groups is even more frequently associated with the presence of malignant cells. The greatest majority of the leucocytes are polymorphonuclears but lymphocytes do appear.

Histiocytes are present in normal smears. Phagocytic histiocytes are not as common as the small histiocyte. These cells are smaller than the inner layer basal cell. Their nuclei are seldom perfectly round, usually being either oval or crescent shape. They have a finely vacuolated cytoplasm whose cell borders are often indistinct (Fig. 4). Foreign body giant cells are included in the group of histiocytes seen in the vaginal secretion. They oc-

Fig. 7.

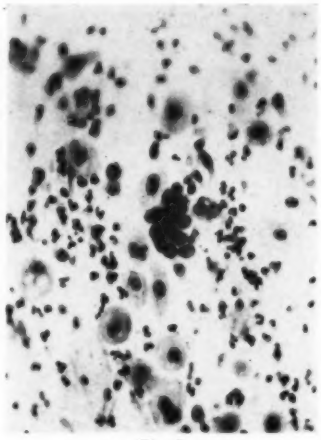

Fig. 8.

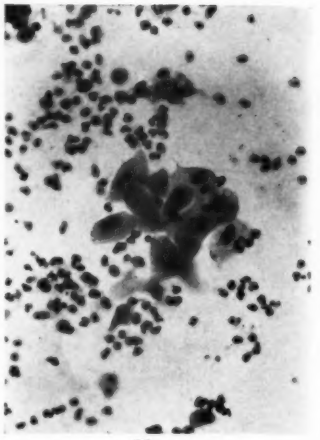

Fig. 9.

Fig. 7. Group of differentiated fiber cells from epidermoid carcinoma of the cervix.

Fig. 8. Group of undifferentiated malignant cells from adenocarcinoma of the cervix.

Fig. 9. Group of basal cells showing beginning elongation of the cells.

cur more infrequently than either of the other two types. They are large cells approximately the size of precornified cells, which have many oval smoothly granular nuclei arranged peripherally (Fig. 5).

The malignant cells as encountered in epidermoid carcinoma of the cervix are of two types, differentiated and undifferentiated depending on how adult the tumor is. The undifferentiated cells are usually smaller than the inner layer basal cell. They have a hyperchromatic nucleus which shows an apparent increase in chromatin material. The cytoplasm consists either of a very narrow rim or an indistinct background. If seen in groups the nuclear size variation is great, and the cellular borders indistinct (Fig. 6). The differentiated cells assume bizarre shapes. They may be the so called "tad-pole" form which show a long thin tail of cytoplasm and a distinct head containing the nucleus. This type is seen rarely. Another type is the fiber cell. This cell is extremely elongated and thin. The nucleus still appears hyperchromatic but it is elongated. These cells closely resemble muscle fiber cells except for their nuclei which are distinctly abnormal (Fig. 7). In the differentiated cells the cytoplasm is usually adequate but it is abnormally distributed.

The malignant cells seen in adenocarcinoma are undifferentiated. They usually occur in tight groups in which the individual nuclei are piled upon one another. Definite cellular borders are difficult to distinguish. Their cytoplasm is a thin rim which may contain vacuoles which are usually small (Fig. 8).

In attempting to study the changes seen in the vaginal smears of women treated with irradiation for carcinoma of the cervix the cases have been divided into four groups. The first group includes those patients who were studied by vaginal smears during their x-ray and radium therapy. The second group includes those with follow-ups beginning from 1 to 6 months after treatment. The third group is composed of those patients whose follow-up began at 6 months to a year following treatment. The fourth group are those patients whose treatment took place a year to fifteen years before the first vaginal smear was taken.

THE EFFECT OF RADIATION ON CELLS AS SEEN IN THE VAGINAL SMEAR DURING TREATMENT—FIRST GROUP

Thirty-five patients with cervical carcinoma have been studied during their course of radiation treatment. There are 4 cases of adenocarcinoma, one of undifferentiated carcinoma

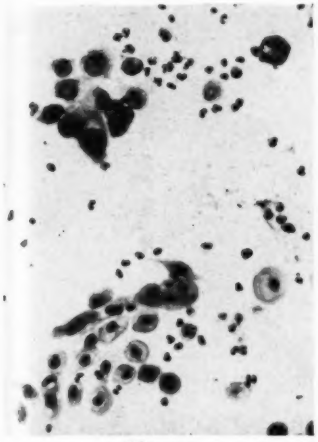

Fig. 10.

Fig. 10. Group at top typical, unradiated, undifferentiated, malignant cells. Group at bottom shows pyknosis of basal cells. Basal cell at right of malignant group demonstrates karyorrhexis of nucleus.

Fig. 11.

Fig. 11. Group of enlarged basal cells. Note proportionate increase in size of nucleus and cytoplasm. Compare with Figure 1.

Fig. 12.

Fig. 12. Abnormal vacuolization of basal cells.

and 30 of epidermoid carcinoma of the cervix. One patient received only radium therapy and 8 only x-ray. The remaining 26 received both x-ray and radium and in every instance the radium was preceded by a course of x-ray. The x-ray treatment was given to 25 by 1200 kilovolt therapy and to 9 by 200 kilovolt therapy. One patient received only 4800 r from the 1200 kilovolt machine, the remainder receiving a dose of approximately 6000 r.

Two cases of bladder carcinoma with no uterine neoplasm have been included in this group as controls. The x-ray fields used in the treatment of carcinoma of the bladder are similar to those used for cervical carcinoma. Thus, we were able to study the effect of radiation on the normal cells of the vaginal and cervical mucosa uncomplicated by the presence of malignant cells.

The patients followed during radiation treatment fall into 2 distinct classes. Class 1 shows definite radiation reaction in all cells. Class 2 shows very little effect in any type of cell either normal or malignant. The possible prognostic significance of these differences will be discussed in a subsequent publication.

The changes in the cellular constituents have been noted from day to day following the beginning of treatment. The first patients studied had daily vaginal smears. However, as the study progressed it was obvious that smears taken at 3 day intervals gave an adequate picture of the changes which occurred. The days indicated in the paragraphs below are counted from the beginning of radiation treatment.

Class 1–Radiation Changes. In the vaginal smear the first effect of radiation is seen in the normal cells. The basal layer of the vaginal and cervical mucosa is affected before any of the other cells show changes. The basal cells, both inner and outer, become aberrant (Fig. 9). They lose their characteristic round appearance and become elongated. These cells must be differentiated from the malignant fiber cell. The nucleus in these aberrant basal cells is still a perfectly normal vesicular nucleus. The malignant fiber cell contains an abnormal hyperchromatic nucleus with very distinct clumps of chromatin. This change in the basal cells is occasionally seen as early as the second day of x-ray treatment but is usually not marked until the 9th or 10th day.

An effect which is seen at the same time as the change in the shape of the basal cells is a change in their staining reaction. Many of the

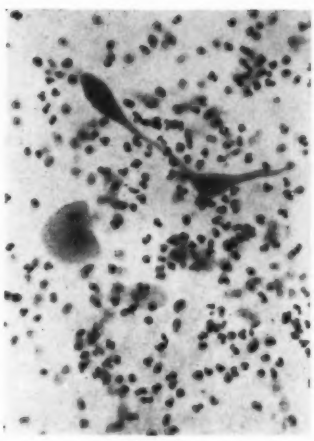

Fig. 13.

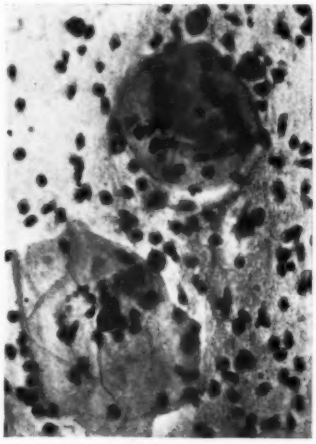

Fig. 14.

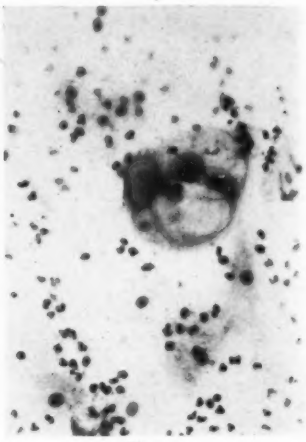

Fig. 15.

Fig. 13. Cell showing one of the bizarre shaped basal cells after radiation.

Fig. 14. Cell at bottom shows tremendous size increase of precornified cell. Compare with Figure 3. Cell at the top shows polymorphonuclear leucocytes on precornified cell.

Fig. 15. Precornified cell with three nuclei showing abnormal vacuolization of the cell.

cells of the basal layer change from a basophilic stain to a brownish stain[1]. This does not occur in all the cells but is a frequent enough occurrence to be a distinct effect. This difference in staining reaction is probably an early sign of degeneration of the cell.

The subsequent changes are primarily in the nucleus of the basal cells. The nuclei become very degenerate. The nucleus may appear as one small pyknotic dot. Often the nuclear membrane disappears and the nuclear material is collected into discrete black clumps, an actual karyorrhexis of the nucleus (Fig. 10). This type of degeneration will occasionally be mistaken for mitoses if care is not taken. A cell in mitosis shows chromatin in fine threads or very small clumps rather than three or four structureless dots. These degenerative changes usually take place from the 10th day of treatment and increase throughout the course of treatment. It should be noted that this reaction in the nuclei of the basal cells is not characteristic of radiation alone. The same degeneration is often seen in advanced atrophy of the genital tract.

Beginning usually around the twelfth day the most striking effect of radiation on the cells of the basal layer is seen. There is a great increase in the size of the cells. They become three to four times their normal size. The change is similar to the ballooning of cells which has been described in histiological sections following radiation treatment. It is important to realize that these "blown-up" cells show no change in the cytoplasmic-nuclear ratio. It remains constant. The nucleus and the cytoplasm, have increased in the same proportion (compare Figs. 1 and 11). The nucleus in one of these large cells is even more finely granular than in the normal. It has a very smooth, speckled appearance in most instances. One should be careful that cells of this kind are not called normal precornified cells. The total size of the cell is often that of precornified cells. Two criteria point to their origin in the basal layer. First, the cytoplasm does not have the true transparency of precornified cells; second, the nucleus is much too big for a normal precornified cell. We have never seen this tremendous ballooning of cells except in smears from a radiated patient.

Another specific change in the basal cells is abnormal vacuolization of the cytoplasm. This usually occurs in cells which have increased in size and is a late effect. It is usually

[1]All smears were stained by Papanicolaou's method. The directions for staining and the constituents of the stain may be found in the monograph by Papanicolaou and Traut or in our first publication.

Fig. 16.

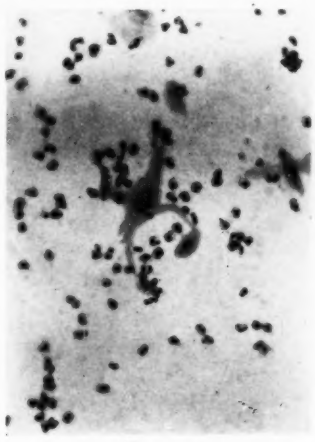

Fig. 17.

Fig. 18.

Fig. 16. Tremendously elongated cell showing degenerative changes in the nucleus.

Fig. 17. Bizarre shape of precornified cell after radiation treatment had been carried out.

Fig. 18. Superficial cell showing polymorphonuclears in the cytoplasm.

not marked until the fifteenth day and increases progressively after that. The cells contain tremendous vacuoles which almost completely fill the cell (Fig. 12). Some of the cells may have smaller vacuoles containing polymorphonuclear leucocytes in the vacuole. This sequence is not so commonly seen in the basal cells, however, as in the precornified.

The last change to occur in the cells of the basal layer is the appearance of very bizarre forms. The cells may be almost any shape. They are usually of the "blown-up" type so the shape is even more striking (Fig. 13). This change is much more pronounced than in the aberrant forms mentioned earlier. The cells may assume dumbbell shape, elongated forms, and tadpole forms. These cells must also be distinguished from the differentiated malignant cell. The nucleus is the distinguishing characteristic. It is large but is smoothly granular and not hyperchromatic, or is very small and pyknotic.

It is important to point out that the changes in the basal cells here noted, are seen only if the control smear before treatment presented basal cells as part of the cell population. If the woman is premenopausal few basal cells are found and the radiation changes seen first are in the precornified cells to be described.

The precornified cells also exhibit changes after radiation. The first reaction to occur in this layer of cells is an increase in size. They become two to three times the size of a normal precornified cell. The cytoplasm and the nucleus increase correspondingly so that the cytoplasmic-nuclear ratio is undisturbed (Fig. 14). This effect has been seen as early as the third day of radiation and as late as the forty-fifth. However, on the average it is apparent about the fifteenth day of treatment.

At about the same time as this increase in size takes place there are beginning changes in the nuclei of the precornified cells. At first the only change is one of size, but very soon the chromatin structure of the nucleus begins to show degenerative changes. Their nuclei become dark, wrinkled, with little structural detail. The nucleus has a dead pyknotic look despite its abnormal size. The nuclear borders are not smooth but very irregular and often the nucleus has contracted sufficiently to leave a space previously occupied by the full sized nucleus. Occasionally although it is not seen as often as in the basal series, the nuclei will become fragmented and will appear only as small dark particles, the nuclear borders having completely disappeared. Two, three, and four nuclei are not uncommon in these pre-

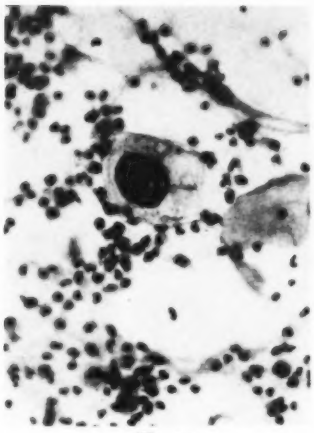

Fig. 19.

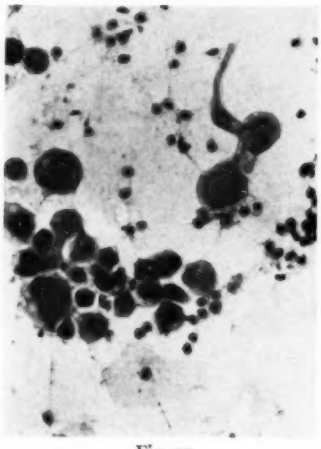

Fig. 20.

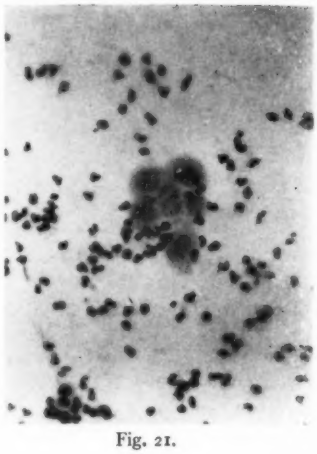

Fig. 21.

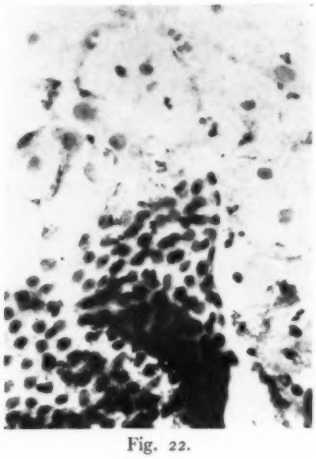

Fig. 22.

Fig. 19. Radiated malignant cell showing increase in size of cell and nucleus and abnormal vacuolization.

Fig. 20. Group of radiated malignant cells showing giant cells and abnormal vacuolization.

Fig. 21. Smear showing enlarged degenerate basal cells.

Fig. 22. A sheet of basal cells seen when vaginal smear is difficult to obtain.

cornified irradiated cells. These multinucleated cells may have the blown-up vesicular type of nucleus or a degenerate one. The presence of more than one nucleus is probably evidence of an amitotic division stimulated by radiation.

At the same time that nuclei begin to exhibit signs of degeneration the cytoplasm also shows evidence of degeneration. The first degenerative sign in the cytoplasm is the appearance of very fine fibers which may occur in concentric circles around the nucleus or may run from the nucleus to the cell border. The most striking effect is the vacuolization. The vacuoles may be very large, occupying the greater part of the cell (Fig. 15).

An effect which occurs immediately after the increase in size of the cells and the change in the nuclei is the appearance of precornified cells of queer shape. These bizarre cells are seen occasionally as early as the 6th day of treatment but usually do not appear until later, around the 18th day. The cells are even more striking than the bizarre basal cells due to their size (Fig. 16). They also may assume any shape. Some become tremendously elon-

gated in some instances stretching across a high dry field. Others may assume tremendous tadpole shapes. Some have long fibers stretching out from the cell almost resembling pseudopodia (Fig. 17).

The last change to occur in the precornified layer is the appearance of polymorphonuclear leucocytes in the cells. This takes place usually around the 20th day of treatment. It has been seen as early as the 10th and as late as the 31st. It is important when looking for this change to be sure that the polymorphonuclear leucocytes are in the cells and not merely on top of the cells. The leucocytes are very numerous often in postradiation smears, and often they clump on a cell almost obscuring the cell beneath them. This takes place early in the course of treatment. However, the actual inclusion of leucocytes within epithelial cells is a later change (Fig. 18).

The cornified cells exhibit all the evidence of postradiation reaction which are seen in the precornified cell except for the changes in the nuclei. Since the nuclei of cornified cells are originally pyknotic, very little change takes place there. The other changes noted apply to the cornified cells as well as to the precornified cells. It should be noted that in radiation smears the precornified cells do not always have a basophilic staining cytoplasm. They very often take an acidophilic stain. As in normal cells the nucleus is the distinguishing characteristic.

A great increase in polymorphonuclear leucocytes is seen very often in the immediate postradiation smears. In all but 3 of the cases the leucocytes increased markedly. In some cases they increase so much that interpretation of the smear is quite difficult since the leucocytes obscure much of the picture. In 3 cases the increase was due to lymphocytes rather than to polymorphonuclear leucocytes. The increase in leucocytes is variable in the time it appears. It may occur immediately after treatment is instituted or it may not occur until much later.

There is some literature on the occurrence of eosinophils in sections of cervical carcinoma. Gill, in 1944, reported that 7.7 per cent of all epidermoid carcinomas of the cervix had a marked eosinophila in the tumor. He believes this may be regarded as of favorable prognostic significance. Unfortunately, in vaginal smears the polymorphonuclear leucocytes are so seldom completely preserved that differentiating between types is usually impossible. One of the cases followed during treatment showed a tremendous number of eosinophils. In all other instances no differentiation could be made as to the type of leucocyte.

An increase in small histiocytes usually follows the increase in leucocytes. The time factor is variable but they appear usually 3 to 5 days after the increase of leucocytes. This increase in small histiocytes was seen in all but 3 of the cases. The response of the phagocytic and foreign body giant cells is variable. A marked response of the phagocytic type was seen in 3 cases and foreign body giant cell reaction in 2.

Evidence of some blood is usually seen in positive smears before radiation. It is a variable factor after treatment is instituted. In some cases the bleeding will stop and the smear be free of any blood. Others show fresh blood, fibrin, or blood pigment.

Class 1. Radiation Effect in Malignant Cells. The malignant cells show pronounced radiation effect as well as do the normal cells of the vaginal and cervical mucosa. The time of the appearance of definite radiation reaction in these cells varies from patient to patient. The malignant cells all show radiation changes usually by the eleventh day of treatment, but occasionally the cells will appear radiated as early as the 8th day. Other cases may not show the complete effect until as late as the 17th day of radiation.

Radiated malignant cells show a good many changes similar to those seen in the normal cells. They increase in size, occasionally as much as four times. Their cytoplasm becomes vacuolated. This vacuolization is especially striking in the small undifferentiated tumor cells which have little cytoplasm. The thin rim of cytoplasm becomes puffed out eccentrically with vacuoles which in some instances are larger than the nucleus (Fig. 19). The radiated malignant cells often contain more than one nucleus, and in many cases may appear as giant cells with 6 to 7 nuclei, prob-

ably again evidence of abnormal division stimulated by radiation (Fig. 20). The appearance of the nucleus is not that of the heavy granular unradiated malignant cells, but rather it is one of complete pyknosis. The nuclei appear dead rather than active. Usually no nucleolus can be made out.

It is often very difficult to say whether a radiated cell was originally malignant or benign. This is especially true of the differentiated malignant cells seen in cervical epidermoid carcinoma. The bizarre cells of both the basal and intermediate layer still have more cytoplasm surrounding the nucleus than do the true differentiated malignant cells. The nuclei of the bizarre basal and precornified group are much more apt to have a washed out smooth appearance than a hyperchromatic, pyknotic one.

Nearly half of the cases described in this group showed an increase of malignant cells after radiation had begun. The time of the increase varied from 3 to 21 days and averaged 9. The remainder of the cases showed a progressive decrease in malignant cells until their final disappearance. It is perhaps interesting to note that 1 of the 2 cases of adenocarcinoma of the cervix in this group showed persistence of malignant cells although they did appear radiated. The cells did not disappear until radium treatment was given. On the average, however, the malignant cells have disappeared by the 24th day after radiation has begun.

Class 2—Little Radiation Change. Not all cervical carcinomas treated by radiation show the change described for the class 1 type of patient. Of the 22 cervical tumors included in this group followed during x-ray treatment, 8 showed a different picture. Six cases were epidermoid carcinoma of the cervix, 1 a papillary adenocarcinoma, and 1 an undifferentiated carcinoma.

Two patients were given palliative doses of x-radiation (4200 r and 2800 r), and no radium. As might be expected these patients showed very little change in any of the cells. Typical unaffected cells persisted during treatment. They showed little evidence of having been affected by x-ray. One of these patients given only palliative therapy showed no effect of radiation at all in the normal cells, and the other only a very slight response at the end of 22 days.

One patient was treated by radium alone (4700 mgm. hrs.). The smears from this patient did show a disappearance of the malignant cells but no change in the normal cells.

The remaining 5 cases had over 6000 r of x-ray and in addition at least 2400 milligram hours of radium. Of these cases 2 show persistent unradiated malignant cells, while 3 had carcinoma cells persisting longer than usual and none of these cells showed any definite change. The smears from these patients contain only a rare normal cell showing radiation reaction, though in these cases the therapy was adequate.

As a control the vaginal smears of 2 cases of bladder carcinoma treated by radiation and uncomplicated by any uterine neoplasm have been studied. The normal cells in the vaginal smear show the same radiation changes as described for the class 1 type of case, and the changes took place at approximately the same time.

THE EFFECT OF RADIATION ON CELLS AS SEEN IN THE VAGINAL SMEAR IMMEDIATELY AFTER TREATMENT TO SIX MONTHS—SECOND GROUP

The 50 patients included in this group are those whose follow-up began immediately after treatment or within 6 months. None of these patients were followed during their treatment and for this reason they have been segregated from the first group, though a good many of the changes described previously are seen in this group also.

Eighteen cases (15 of epidermoid carcinoma and 3 of adenocarcinoma) presented moderate to marked reaction to radiation as shown by the cells in the vaginal smear. A reaction was considered as moderate if over half the epithelial cells showed radiation change and the malignant cells had disappeared. A reaction was called "marked" if it was difficult to find any cells not showing radiation reaction. The reaction is identical with that described for the class 1 type in the first group.

The striking effect of radiation on the cells of the vaginal secretion is not a lasting one.

The number of cells showing increase in size, vacuolization, bizarre shape, and invasion of the cytoplasm by leucocytes, rapidly diminishes. Two months after treatment an occasional cell showing these changes is seen. By 3 months such cells are even more difficult to find and in many instances the specific effects of radiation have disappeared by this time. The cornified and precornified are either completely normal or occur in groups without clear nuclear borders. As might be expected the nonspecific changes seen in the basal series persist for a much longer period. No definite time limit has been found for this effect to disappear. The basal cells have large active vesicular nuclei and often a vacuolated cytoplasm. They may have a normal round contour or be aberrant, assuming an elongated form. Leucocytes and histiocytes may or may not be present, but usually the smear has a much cleaner appearance than seen earlier.

Thirty-two patients (27 with epidermoid carcinoma, 4 with adenocarcinoma, and 1 with adenocanthoma) showed little or no reaction to radiation in the epithelial cells of the vaginal smear. The response in the malignant cells was variable. Fourteen patients showed a disappearance of the malignant cells while the remaining 18 showed persistent cancer cells. The smears usually show perfectly normal or degenerate cornified and precornified cells and a rare active basal cell. This is similar to that seen in the first group, class 2.

THE EFFECT OF RADIATION ON CELLS AS SEEN IN THE VAGINAL SMEAR SIX MONTHS TO A YEAR AFTER TREATMENT—THIRD GROUP

The 19 patients included in this group are those whose follow-up by vaginal smear began 6 months to a year after radiation treatment was finished. This group necessarily overlaps the previous group somewhat in time element.

Eleven (10 epidermoid carcinoma and 1 adenocarcinoma) out of this group show the expected picture. The vaginal smear consists of perfectly normal or degenerate (cellular borders not distinct) cornified and precornified cells, and aberrant basal cells with active vesicular nuclei. Small histiocytes and leucocytes are present but in variable numbers. Four patients showed foreign body giant cell reaction. All the specific effects of radiation have disappeared by this time.

Four patients (3 with epidermoid and 1 with adenocarcinoma) show no reaction of any kind. The smears are perfectly normal ones and any distinguishing characteristics are absent.

There are 4 patients (3 with epidermoid carcinoma and 1 with adenocarcinoma) who showed aberrant basal cells, increase in polymorphonuclear leucocytes, evidence of blood, and malignant cells. These, of course, are postradiation recurrences. It is difficult to see any difference between these 4 and the rest of the group except for the presence of malignant cells. The epithelial cells in these smears are aberrant basal cells with active vesicular nuclei.

THE EFFECT OF RADIATION ON CELLS AS SEEN IN THE VAGINAL SMEAR FROM ONE TO FIFTEEN YEARS AFTER TREATMENT—FOURTH GROUP

The 102 patients included in this group have been followed by vaginal smear beginning at 1 year to 15 years after treatment by radiation. It is in this group that the radiation has varied more than in previous ones since the time interval is of much longer duration. Radiation treatment has varied considerably during the past 15 years so necessarily the cases are not exactly comparable to the first three groups described. However, they are an interesting group in which to study the prolonged effects of x-ray and radium on the cells of the vaginal and cervical mucosa.

Twenty-nine of these patients were given radium alone and these include all those whose follow-up is longer than 10 years. These are included in the groups to be described, since they show no distinguishing characteristics.

This group of cases falls into three separate categories if divided by the type of cell found in the smear. Approximately one-third of the cases show only basal cells, one-third precornified cells and basal cells, and the remainder cornified, precornified, and an occasional basal cell. This is not an age difference since the three groups do not differ significantly in age.

The smears which show basal cells alone have three variations. They may consist entirely of enlarged degenerate cells sometimes seen in normal atrophic smears of menopausal women (Fig. 21). These are basal cells whose nuclei are degenerate and large. The staining reaction of the nuclei is not even and often has a blotchy washed out appearance. The cytoplasm also stains irregularly. This is not diagnostic of radiation but is seen as well in the atrophic smears from normal postmenopausal women. Another type of smear seen is one in which all the cells are aberrant and have large vesicular nuclei. The cells have elongated forms occasionally with rather long tails. It is often difficult to find any normal round basal cells. These queer forms are one of the most difficult types to distinguish from malignant cells. The nuclei of these cells, though active, are rarely as hyperchromatic as malignant nuclei. The third type is a smear in which sheets of basal cells are seen. The cells do not shed singly but come off in great clumps. These may be very confusing, since at first glance, especially when cell borders are indistinct, they are not unlike cancer cells except for their regularity in size (Fig. 22). These cell groups usually occur when the smear has been difficult to obtain. If an attempt is made to secure a vaginal smear when the mucous membrane is very dry and atrophic, the pipette is apt to aspirate cells from the mucosa directly and not those cells which have been shed previously. This smear is not representative of the vaginal secretion. A small percentage of patients after radiation have no vaginal secretion. If secretion cannot be obtained with ease, it is perhaps better not to attempt to get a smear.

Of this fourth group approximately one-third show only precornified cells and basal cells in the vaginal smear. The cells may appear perfectly normal or they may be degenerate with indistinct cellular borders. Cornified cells may also be present. However, it is very rare (3 of the smears of this group) to see a normal smear of precornified and cornified cells this long after radiation.

Leucocytes are seen in this group of post-radiation smears, but their numbers are variable. Small histiocytes occur frequently. No evidence of foreign body giant cell reaction was seen. Fresh blood is encountered occasionally, and is probably due to the breaking of small adhesions in the vagina. Blood pigment is a much more infrequent finding.

Eight of these 102 patients represent recurrence of their original disease. Five show typical undifferentiated carcinoma cells with no evidence of radiation reaction in the normal cells. Three show undifferentiated malignant cells and very active basal cells. The malignant cells are as those described for unradiated undifferentiated cells. They show no evidence of having originated from a tumor previously radiated.

DISCUSSION

The changes seen in the individual cells, both normal and malignant, which are desquamated into the vaginal secretion are quite comparable to those previously described by many authors in the study of biopsy specimens from irradiated patients. Of course, there are some differences since in a study of the vaginal smear a representative group of all types of cells is seen, while a biopsy is limited to that area which has been removed. Another distinguishing factor between the two methods is that the vaginal smear deals only with the cells on the surface while the biopsy shows the changes much deeper.

Dustin, Frola, and Arneson and Stewart all have described the pyknosis of the nuclei of the cells in biopsy material from patients with carcinoma of the cervix. Pyknosis of the nuclei is marked in the radiation response as seen in the vaginal smear. The cells from the basal layer show a marked pyknosis which often is one of the prolonged effects and among the last to disappear.

Dustin, Meigs and Parker (6), and Frola emphasize the atypical mitoses which occur in the malignant cells during treatment. Mitoses are rarely seen in the vaginal smear. This is true not only of the irradiated cases but untreated cases as well. Whether cells in mitosis go on to complete the division after being desquamated or whether the majority of the cells in mitosis are deep and not likely to slough is not known. Evidence of abnormal mitoses is seen in the vaginal smear in the abnormal malignant giant cells which are often

encountered after irradiation. A good many of the normal cells also show division of the nucleus with no division of the cell.

Frola emphasizes the fact that after radiation there is a subsequent maturation of the undifferentiated cells to mature cells with sharp nuclear borders. We have not interpreted any cells in this light. The bizarre shaped cell, which in an untreated carcinoma might be classified as a differentiated malignant cell, has been interpreted rather as a normal cell which has been so affected by radiation as to be almost indistinguishable from an unradiated differentiated malignant cell. This may be a mistake in interpretation but it is made on the basis that the cases of bladder carcinoma showed these bizarre cells although there were no malignant cells present in the genital tract. We have concluded that their unusual shapes, nuclear and cell size increase and, in occasional instances, the hyperchromatic but pyknotic appearance of the nucleus is due rather to radiation effect on normal cells than to any maturation process stimulated by radiation. It is for this reason that it has become the policy of our laboratory not to call postradiation smears positive unless typical healthy undifferentiated malignant cells are seen. To one unfamiliar with radiation changes the bizarre cells and the queer pyknotic, huge nucleus of the irradiated normal cells will often be confusing and lead to an error in diagnosis.

Frankle and Amreich have described the swelling of cells during radiation therapy. This is very evident in vaginal smears. The size increase of cells both normal and malignant is very conspicuous. These same authors mention vacuolization of the cells. This effect is also seen in vaginal smears. It is one of the responses seen in marked reaction of the cells to irradiation. Frola, and Arneson and Stewart mention the increased leucocytic reaction and the foreign body giant cell response of the cervical tissue to roentgen therapy. These reactions have both been described here as they are seen in the vaginal secretions from irradiated cervical malignancy.

It is evident that the correlation of the numerous changes seen in the past in the study of irradiated cervical cancer by biopsy and the changes seen in the vaginal smear are quite comparable. The pyknosis and degeneration of the nuclei, the swelling and vacuolization of the cytoplasm, the evidence of abnormal mitoses, and finally the leucocytic infiltration and foreign body giant cell reaction are all seen in the vaginal secretion as they are in the biopsy material. The vaginal smear is a much simpler way of studying the reaction of both tumor and normal cells. It is difficult to do serial biopsies on treated patients. Toward the end of treatment the biopsy may show only necrosis and no viable tissue, thus making interpretation impossible. The vaginal smear, on the other hand, is obtained with great ease, as often as desired, for the whole course of treatment. It has the additional advantage of giving possibly a more accurate picture since the entire cell population of the cervix and vagina is represented, not merely that of one specific area. The vaginal smear represents a unique and possibly important method of studying radiation reaction in cervical carcinoma.

SUMMARY

Two hundred and six cases of cervical carcinoma in which patients were treated by radiation have been studied by vaginal smear. Both immediate and late changes in the cells in the vaginal secretion have been described. Correlation with studies by biopsy have been discussed. The applicability of this method for study of radiation effect in cervical cancer has been suggested and emphasized.

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THE EFFECT OF RADIATION ON VAGINAL CELLS IN CERVICAL CARCINOMA

II. The Prognostic Significance

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A SIMPLE method of determining what effect radiation has on carcinoma of the cervix during and immediately after treatment would be of great practical value. The present methods of evaluating results are exceedingly cumbersome. Most advances in roentgen therapy of this disease have been determined on the survival rates of a certain group of patients as balanced against another group treated differently. If a method could show that at the end of treatment a satisfactory or unsatisfactory result could be expected, instead of the necessity of waiting for a 5 year survival rate, the number of cures might be appreciably increased by modification of the present methods of treatment. We believe that the study of the response of cervical tumors to radiation treatment by means of vaginal smear may represent a method of practical value in the early prognosis of cervical cancer.

Many studies have been done in an attempt to correlate biopsy data with possible prognostic value. In 1936 Warren, Meigs, and associates published a series of 70 cases of carcinoma of the cervix studied by means of repeated biopsies during radiation treatment. They found that if the tumor showed marked radiation effect and there were changes in the stoma consistent with radiation reaction, the survival rate was increased. If, however, the tumor showed little effect and the stroma little or none, the patients did very poorly.

Other authors have attempted to correlate the grade of tumor with the clinical response. Stewart and Farrow, in 1940, reported that there was a marked difference in the response to x-ray and radium of the same grade tumors. In their opinion single biopsies were not very valuable in judging the actual response. They conclude that a more satisfactory prognosis can be made on the basis of the clinical type of tumor, i.e., the cauliflower growth does much better than the crater-like type of lesion.

An interesting study has been reported recently by Glucksmann and Spear. They have attempted to quantitate the radiation response in treatment. The authors emphasize that great care be taken to secure the tissue for biopsy from the growing edge of the tumor. These biopsy specimens were sectioned and areas which showed papillary projections growing into normal tissue were the ones chosen for study. Quantitative counts were done on four types of cells in these areas: (1) the cells in mitosis, (2) resting carcinoma cells, (3) differentiating cells, (4) degenerating cells. The cells in mitosis disappeared soon after treatment was instituted, the resting carcinoma cells persisted longer than the cells in mitosis, but these too gradually disappeared. The differentiating cells increase, finally disappearing after treatment is ended. The degenerating cells increase throughout the treatment and persist for sometime afterward. Thus if the degenerating cells and carcinoma cells are plotted against the days of treatment a graph is obtained in which the two lines cross since as the degenerating cells increase the carcinoma cells disappear. In an unfavorable response the carcinoma cells both in mitosis and those resting remain, and the degenerating cells do not increase, giving a graph where the lines are parallel.

In a previous publication the effect, both immediate and prolonged, of radiation on the cells seen in the vaginal secretion of patients with carcinoma of the cervix has been described. In this paper an attempt has been made to correlate these findings with the clinical picture and the end-result of treatment.

Of the 206 cervical carcinomas studied in the previous paper, only 73, whose follow-ups were of sufficient length of time (first and

second groups), are included in this study. The changes seen during and immediately following treatment are the important ones as far as any prognostic value is concerned. As yet no correlation has been obtained in the appearance of the vaginal smear months or years after treatment.

In our first paper on the changes due to radiation as seen in the vaginal smear, we described the cases followed during and immediately after treatment as falling into two definite classes. The first class is that which shows the following changes. The normal cells: the basal cells first increase in size, then show signs of degeneration and, toward the end of treatment, show marked degenerative changes such as vacuolization of the cytoplasm and marked pyknosis or karyorrhexis of the nuclei. The precornified cells show the same changes though these occur later than those seen in the basal layer. The degeneration of the nucleus is not as prominent in the precornified cells as in the basal. The nuclei of the precornified cells often have a smooth washed out appearance. The cornified cells increase tremendously in size, and there is much cytoplasmic degeneration, but since the nuclei of these cells are originally pyknotic there is no change there. The smears usually show a progressive leucocytosis and an increase in small histiocytes. Occasionally phagocytic histiocytes appear and in a few cases foreign body giant cells were seen. Malignant cells: these usually persist until the tenth or eleventh day of treatment. They sometimes increase in numbers and then disappear, but more often show a gradual decrease. The time of their disappearance is unimportant. More important is the gradual decrease. The malignant cells of class I show pronounced radiation changes. They are often multinucleated giant cells, probably evidence of amitotic division. They show the same degenerative changes as described for the normal cells, increase in size, vacuolization, and finally a smooth washed out appearance to the nucleus, pyknosis or a complete breaking up of nuclear material.

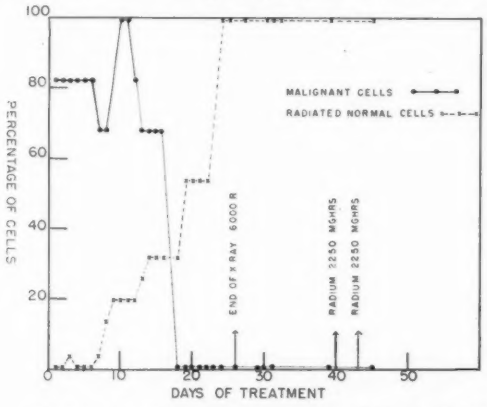

Chart 1. A good response to radiation (Case 6 in Table III) showing a complete disappearance of malignant cells by the 18th day and a maximum radiation effect in the normal cells by the 23rd day. It should be noted that the percentage of malignant cells is based on a scale in which 100 per cent equals the maximum incidence of these cells encountered in any of the smears on this case, while the radiation effect is based on 100 per cent equaling a response in all normal epithelial cells.

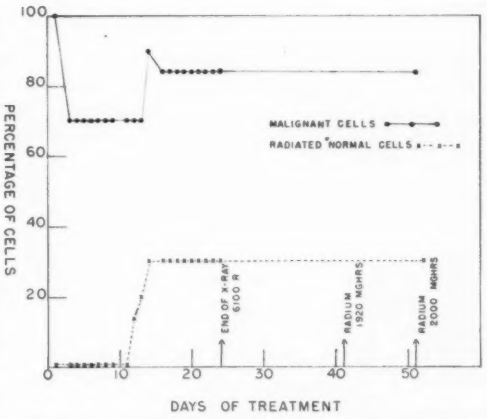

Chart 2. A poor response to radiation (Case 19 in Table IV). There is very little diminution in the number of malignant cells seen and the normal epithelial cells show only a slight response to radiation.

Chart I shows a typical case which falls into class I. The approximate percentage of normal cells showing radiation reaction and the approximate percentage of malignant cells present, whether healthy or irradiated, are plotted against the days of treatment. It is important to note that the chart is *approximate* and does not represent absolute quantitative data. It is difficult to do accurate cell counts on vaginal smears since many fields are too thick to count individual cells and only thin areas could be used. The chart merely

TABLE I.—GOOD RESPONSE GROUP

Stage	No. of cases	Well	Dead	No follow-up
I	6	6	0	0
II	21	16	3	2
III	6	4	1	1
IV	3	2	1	0
Total	36	28	5	3

indicates subjective conclusions regarding individual smears. If on extensive search no malignant cells were found either healthy or irradiated, the percentage was recorded as zero. If on examination of the slide it was difficult to find any normal cells not showing advanced radiation changes the radiation effect in the normal cells was recorded as 100 per cent. The points other than these on the curve are distinctly personal interpretation of the entire individual smear.

As can be readily seen from the chart the number of malignant cells gradually decreases as the number of normal cells showing radiation response increases. This we regard as a marked response to radiation therapy. Occasionally marked radiation response is shown in the normal cells, yet some radiated malignant cells will persist though they have decreased. This we still regard as a favorable response since the reaction in the normal cells appears to be the most important in the prognostic value. We have not had a case in which the normal cells showed marked radiation response and the malignant cells showed no decrease and appeared unradiated. This type of chart is almost identical with that characteristic of a good response published by Glucksmann and Spear on quantitative cell counts of biopsy material in irradiated cervical carcinoma.

The clinical course of the patient shown in Chart 1 is as follows: this 27 year old, quadripara, entered the hospital with a complaint of vaginal bleeding for 6 months. She was found to have a stage III carcinoma of the cervix. The tumor was an epidermoid carcinoma grade II. She was given 6000 r through two portals over a period of 20 days. After x-radiation she was given two separate doses of radium totaling 4500 milligram hours. Fifteen months after treatment a biopsy was done of tissue from a small raised area in the vagina. The pathological report on this tissue was papilloma. Patient has been well and symptom free for 2 years since treatment.

In the class 2 type of reaction there is very little reaction in the normal cells. The percentage of cells showing radiation reaction is very small. The malignant cells do not disappear. Chart 2 shows a graph which is seen in the class 2 type of patient. This is an entirely different picture from that seen in Chart 1. The lines are parallel. There is little evidence of any effect of radiation either in normal or malignant cells. This type of chart we regard as a poor response to radiation and again it is almost identical with that reported by Glucksmann and Spear as characteristic of an unfavorable response.

The clinical course of the patient shown in Chart 2 is as follows: this 39 year old, tripara entered the hospital with the chief complaint of postcoital bleeding of 6 months' duration. The tumor was an epidermoid carcinoma grade II with a clinical classification of stage III. She received 6200 r of 1200 kilovolt x-radiation though two portals which was followed by a total of 3920 milligram hours of radium in two separate doses. Patient died of her disease 9 months after the termination of treatment.

RESULTS OF STUDY

Seventy-three cases are included in this study. Of these 59 were histologically epidermoid carcinoma, 11 adenocarcinoma, and 3, undifferentiated carcinoma. There has been no correlation between the type or grade of tumor and the subsequent response to radiation.

The cases have been divided into poor and good responses. Thirty-six were judged as

TABLE II.—POOR RESPONSE GROUP

Stage	No. of cases	Persistent disease, Recurrence or dead	Well	No follow-up
I	0	0	0	0
II	9	8	1	0
III	19	18	1	0
IV	7	6	1	0
Unknown	2	2	0	0
Total	37	34	3	0

TABLE III.—GOOD RESPONSE GROUP

Patient	Age	Symptoms	Type and grade of tumor	Stage of disease	Treatment	Biopsy after treatment	Vaginal smear response	Follow-up
1. R.C. 439665	32	Postcoital bleeding	Epi. II	2d	6000r 3900 mghrs.		Good	None
2. E.R. 439680	60	Bleeding 6 mos.	Epi. IV	2d	6000r 4500 mghrs.		Good	Well-2 yrs.
3. M.R. 429551	61	Vaginal bleeding	Epi. ca.	1st	6000r 4500 mghrs.	Chronic inflammation	Good	Well-2 yrs.
4. R.A. 471575	47	Postcoital bleeding 6 mos.	Epi. III	2d	6200 r 4000 mghrs. Taussig operation 6 mos. after radiation	Epi. ca. Hypogastric node at Taussig	Good	Well 14 mo.
5. J.G. 483169	55	Bleeding 4 mos.	Epi. III	2d	6200r 4000 mghrs.	Acute Inflammation and necrosis	Good	Dead
6. M.K. 438206	27	Bleeding 6 mos.	Epi. II	3d	6000r 4500 mghrs.	15 months after treatment: papilloma	Good	Well 2 yrs.
7. M.J.	75	Episode of vaginal bleeding	Adeno.	2d	6000r 4500 mghrs.	Chronic Inflammation	Good	Dead
8. A.R. 439656	45	Bleeding 6 mos.	Epi. III	3d	7200r 4000 mghrs.	Acute and chronic inflammation	Good	Well 2 yrs.
9. A.T.	65	Bleeding 6 mos.	Adeno.	2d	6000r 3500 mghrs.	Adenocarcinoma Radiation reaction	Good	Well 2 yrs.
10. L.M. 483419	54	Bleeding 6 days	Epi. II	2d	7800r		Good	None
11. P.V. 449303	49		Epi. III	3d	4200r 1680 mghrs.		Good	None
12. L.E. 448883	47	Spotting	Epi. III	2d	6000r 4440 mghrs.	Epi. carcinoma Chronic inflammation	Good	Well 2 yrs.
13. M.C. 448361	50	Bleeding 3 days	Epi. III	1st	6000r 4400 mghrs.	Chronic inflammation	Good	Well 1 yr.
14. M.R. 439056	33	Bleeding 3 wks.	Adeno.	2d	6000r 4000 mghrs.	Chronic inflammation	Good	Well 16 mos.
15. L.P. 469056	69	Bleeding 6 mos.	Epi. II	2d	6300r 2000 mghrs.	Epi. carcinoma Chronic inflammation	Good	Well 11 mos.
16. L.T. 464874	61	Bleeding 2 mos.	Epi. III	2d	6000r 4500 mghrs.	Epi. carcinoma Acute and chronic inflammation	Good	Well 10 mos.
17. W.M. 503552	57	Bleeding 4 yrs.	Epi. III	4th	2100r 3750 mghrs.	Epi. carcinoma	Good	Well 5 mos.
18. C.A. P. 21896	34	Intermenstrual bleeding	Epi. II	2d	4800r 3045 mghrs.	Epi. carcinoma	Good	Well 16 mos.
19. A.C. P. 21988	71	Bleeding	Epi. II	2d	6600r 4500 mghrs.	Epi. carcinoma showing marked radiation reaction	Good	Well 1 year
20. M.D. P. 21936	47	Bleeding 5 mos.	Epi. III	3d	3700r 4500 mghrs.	Foci of residual epi. carcinoma showing radiation reaction	Good	Well 18 mos.
21. A.M. P. 22017	51	Bleeding 2 yrs.	Epi. II	2d	2200r 3300 mghrs.	Residual tumor showing radiation reaction	Good	Well 18 mos.
22. M.S.	56	Bleeding	Epi. Ca	3d	2300r 4500 mghrs.	Radiation showing scattered cells	Good	Dead
23. M.C. 409627		Bleeding	Adeno	1st	6300r ? amount of radium	Carcinoma. Radiation effect	Good	Well 6 mos.
24. M.P. 475340	50	Bleeding 8 mos.	Epi. III	2d	6000r 4000 mghrs.	No evidence of malignancy	Good	Well 11 mos.
25. A.S. 441145	49	Bleeding 6 mos.	Epi. III	2d	Exact amount not known		Good	Well 18 mos.
26. A.L. 429781	60	1 period of postmenopausal bleeding	Epi. III	1st	6000r 4120 mghrs.	No evidence of malignancy	Good	Well 27 mos.

TABLE III.—GOOD RESPONSE GROUP—Continued

Patient	Age	Symptoms	Type and grade of tumor	Stage of disease	Treatment	Biopsy after treatment	Vaginal smear response	Follow-up
27. M.S. 439876	56	Bleeding 2 wks.	Epi. II	2d	6000r 4500 mghrs.	Acute inflammation necrosis	Good	Died 7 mos.
28. M.R. 442199	55	Postcoital bleeding	Epi. II	2d	6000r 4590 mghrs.	Acute and chronic inflammation	Good	Well 19 mos.
29. L.B. P. 10091	40	Irregular bleeding	Epi. ungraded	1st	10,000r 5000 mghrs.		Good	Well 3 yrs.
30. W. P. 13115	43	Spotting between periods	2nd recurrence of adeno.	4th	Previous treatment 3600r present treatment 7500r	Adenocarcinoma highly malignant	Good	Persistent disease present 15 mos.
31. S.H. P. 22013	29	Bleeding 6 mos.	Epi.	1st	4800r 4355 mghrs. Wertheim hysterectomy	? residual tumor cells	Good	Well 15 mos.
32. D.C. P. 21866	33	Spotting 6 mos.	Epi. II	2d	2350r Taussig operation 2950 mghrs.	Residual tumor showing radiation reaction	Good	Well 18 mos.
33. M.F. 473195	60	Profuse watery discharge	Epi. III	3d	6000r 4050 mghrs.	Acute inflammation and necrosis	Good	Well 1 yr.
34. L.S. 509225	58	Bleeding 1 mo.	Epi. II	2d	6000r 4000 mghrs.		Good	Well 4 mos.
35. K.L. 172301	67	Spotting 1 yr.	Epi. II	4th	6000r 4000 mghrs.		Good	Well 8 mos.
36. O.W. 465187	63	Right lower quadrant pain	Epi. III	2d	6000r 4930 mghrs.	Carcinoma. Radiation effect	Good	Well 17 mos.

good results. Of these, 28 patients are living and well with no evidence of persistent disease or recurrence. Five patients are dead. We have been unable to follow 3 patients. Table I shows the good response group divided by clinical stage of disease.

Thirty-seven cases were classified as poor responses. Of these 26 are dead, 8 have persistent disease or recurrence and 3 are living. Of these 3, 2 have not been examined during the past year but they are known to be alive. Whether they have persistent disease or not is, of course, in doubt, but we have classified them as well. Table II shows the poor response group divided by clinical stage of the disease.

If Tables I and II are compared it will be readily seen that there is correlation between the prognosis by vaginal smear and the clinical stage of the disease. Both the groups in stage I and stage IV are too small to be of a great deal of significance. However, they are reversed as to prognosis both by vaginal smear and clinical response. Stage II shows a majority of the cases in the good response groups, and in stage III the cases in the poor response group are in the majority.

Tables III and IV give in detail the cases included in this study. The age, duration of symptoms, type and grade of tumor, stage of disease, amount of treatment, biopsies after radiation, response by vaginal smear, and follow-up are all listed.

Though in a series as small as this, statistics of error are not of very great value it is perhaps of interest to point out that if the cases with no follow-up are excluded from the series the prognostic accuracy of the vaginal smear in carcinoma of the cervix is 88 per cent. Glucksmann reported an accuracy of between 80 per cent and 86 per cent in a longer series by means of quantitative counts of biopsy material.

It should be mentioned that the follow-up on this series is not as long as would be most desirable in a study of this kind. The longest follow-up is 3 years, and several patients have been followed-up less than a year. It is fairly obvious that there may be patients who have been classified as good responses who may yet have recurrences. However, the results in the poor response group are such that the length of time of the follow-up is less important. This fact for the time being at least would seem to indicate that a greater importance be attached to a poor response than a good response.

TABLE IV—POOR RESPONSE GROUP

Patient	Age	Symptoms	Type and grade of tumor	Stage of disease	Treatment	Biopsy after treatment	Vaginal smear response	Follow-up
1. M.K. 486497	55	Bleeding 4 mos.	Epi. IV	3d	6000r 4520 mghrs.		Poor	Dead 8 mos. after treatment
2. M.D. 359456	52	Vaginal bleeding. Recurrence of disease treated by radium-1932	Undifferentiated	2d	6000r 1500 mghrs. in 1944		Poor	Dead 5 mos. after treatment
3. L.S. 438516	46	Vaginal bleeding 3–4 wks.	Epi. III	2d	6000r 3900 mghrs.		Poor	Dead 7 mos. after treatment
4. A.W. 422476	46	Bleeding 3 wks. Wertheim operation 1943 Recurrence 1944	Epi. III	2d	6000r 3900 mghrs.		Poor	Dead 4 mos. after treatment
5. M.B. 450936	55	Pain in hip 10 mos. No bleeding	Epi. II	3d	4500r 4400 mghrs.	Necrosis	Poor	Dead
6. M.H. 440955	40	Bleeding 8 wks.	Epi. IV	2d	6000r 4100 mghrs.	Acute and chronic inflammation	Poor	Well 8 mos. No follow-up since
7. D.S. 483843	47	Bleeding 1 mo.	Epi.	?	6000r 4620 mghrs.		Poor	Dead 1 mo. after treatment
8. B.S. 359809	49	Bleeding 6 yrs.	Epi. III	3d	7200r 4400 mghrs.	Acute chronic inflammation	Poor	Dead 12 mos. after treatment
9. M.E. 443037	44	Bleeding 4 mos.	Epi. III	2d	4000r 4500 mghrs.	Acute inflammation	Poor	Dead 7 mos. after treatment
10. K.D. 229221	47	Bleeding 4 mos. Recurrence of disease treated by x-ray in 1938	Epi. carcinoma	3d	6200r in 1938 2200r in 1944		Poor	Dead 15 mos. after treatment
11. M.R. 448198	54	Bleeding 3 yrs.	Epi. III	3d	6000r 3860 mghrs.	Acute and chronic inflammation	Poor	No exam. but known to be alive 2 yrs. after treatment
12. E.K. 124387	43	Severe attacks of vomiting. No bleeding	Epi. III	3d	6000r 4020 mghrs.	Acute and chronic inflammation	Poor	Died 5 mos. after treatment
13. M.C. 451643	29	Bleeding 3 mos.	Epi. III	2d	6000r 4500 mghrs.		Poor	Dead 19 mos. after treatment
14. L.B. 494748	37	Bleeding 10 mos.	Epi. III	3d	6000r 4500 mghrs.	No diagnostic abnormality	Poor	Persistent disease present 7 mos. after treatment
15. A.M. 499432	42	Bleeding 2 wks.	Epi. II	4th	6000r 4500 mghrs.	Acute inflammation	Poor	Persistent disease present 6 mos. after treatment
16. C.T. 340999	51	Spotting 17 mos.	Epi. III	4th	6000r 3700 mghrs.		Poor	No evidence of disease 2 yrs. after treatment
17. A.D. Pr. pt. 10614	70	Bleeding	Adenocarcinoma	3d	1500r 3700 mghrs.	No evidence of malignancy	Poor	Recurrence of disease 2 yrs.
18. H.D. 425174	40	Bleeding 6 months Wertheim operation 1943. Recurrence 1945	Epi. III	3d	6400r 14 mos. postoperatively		Poor	Persistent disease present
19. R.K. 440757	39	Bleeding 6 mos.	Epi. II	3d	6200r 3920 mghrs.	Acute and chronic inflammation	Poor	Dead 10 mos. after treatment
20. M.F. 435332	66	Bleeding 1 mo.	Adenocarcinoma	3d	4000r	Adenocarcinoma	Poor	Dead 11 mos. after treatment
21. E.F. 458600	56	Bleeding 6 mos.	Epi. IV	3d	4100r		Poor	Dead 3 mos. after treatment
22. N.T. 494767	67	Bleeding 4 mos.	Adenocarcinoma	4th	6000r 4500 mghrs.	No evidence of malignancy	Poor	Dead
23. V.C. Pr. pt. 10607	57	Bleeding 1 mo.	Epi. II	3d	6000r 4968 mghrs.		Poor	Died 18 mos. after treatment
24. D.A. Pr. pt. 10896	34	Bleeding 6 mos.	Epi. carcinoma	3d	5200r 3115 mghrs.	No evidence of malignancy	Poor	Dead 4 mos. after treatment
25. E.T. Pr. pt. 10908		Bleeding 14 mos.	Epi. III	4th	x-ray, ? am't 4000 mghrs.		Poor	Recurrence 16 mos.

Pr. pt., private patient

TABLE IV.—POOR RESPONSE GROUP—Continued

Patient	Age	Symptoms	Type and grade of tumor	Stage of disease	Treatment	Biopsy after treatment	Vaginal smear response	Follow-up
26. D.V. pr. pt. 11024	51		Epi. III	4th			Poor	Dead
27. M.M. 452067	77	Bleeding 6 mos.	Epi. III	3d	6000r 4500 mghrs.	Chronic inflammation	Poor	Recurrence 21 mos. later
28. D.T. 491046	36	Bleeding 4 mos.	Epi. IV	3d	6000r 3960 mghrs.		Poor	Dead
29. B.H. P. 21025	58	Bleeding 8 mos.	Epi. II	3d	7600r 3030 mghrs.		Poor	Died 15 mos. after treatment
30. S.B. P. 22098	61		Adenocarcinoma	2d	6400r 4540 mghrs.		Poor	Died 1 yr. after treatment
31. P.G. P. 22034	52	Severe pain lower back and pelvis	Epi. II	Unknown	8400r		Poor	Died 9 mos. after treatment
32. C.V. P. 21926	74	Bleeding 2 yrs.	Adenocarcinoma	2d	2800r		Poor	Recurrence 10 mos.
33. M.P. P. 21849	37	Vaginal discharge	Undifferentiated carcinoma	4th	6400r 4660 mghrs.	Marked radiation reaction of stroma and tumor. 2nd biopsy, marked response of stroma, poor effect on tumor	Poor	Died 5 mos. after treatment
34. M.W. 482066	49	Bleeding 3 mos.	Undifferentiated	4th	6200r		Poor	Died 5 mos. after treatment
35. B.T.	30	Discharge 3 mos.	Epi. III	3d	8200r		Poor	Died 5 mos. after treatment
36. M.H.	43	Bleeding 13 mos.	Adenocarcinoma	3d	6000r		Poor	Died 4 mos. after treatment
37. G.P.	72	Bleeding 1 yr.	Epi. III	2d	6000r 3200 mghrs.		Poor	Persistent disease present

DISCUSSION

Many authors have shown that a correlation between radiation response and prognosis could be obtained by studying radiated tissue. Glucksmann and Spear's recent work on biopsies from the growing edge of tumors which have been irradiated confirms the impression that the radiation response in normal and malignant cells is of great importance in the evaluation of the final result of radiation treatment.

The method of biopsy in the study of radiation response is both time consuming and expensive. It is impossible from a practical standpoint in most clinics to make biopsy studies of patients once a week during their entire course of therapy. Furthermore as treatment progresses, biopsies are difficult to obtain and during the later part of treatment may show only necrotic tumor if care is not taken.

We feel that the vaginal smear method represents a more practical method for following patients during radiation therapy. The vaginal smear is easy to obtain. Technicians can be taught easily to take satisfactory smears. Smears may be taken daily if desired. Another distinct advantage of the vaginal smear is that a representative group of all the cells, both normal and abnormal, of the cervical and vaginal mucosa are seen. For this reason the total effect of radiation reaction can be perhaps more accurately determined.

The results as shown by our figures in this series of 73 cases are significant enough in our opinion to suggest to the clinician the vaginal smear as a practical approach to the problem of radiation response of cervical carcinomas. If by a study of the vaginal secretion the immediate response of the tumor to radiation can be determined, the treatment of cervical carcinoma may be made more effective. If a case is a borderline surgical risk and has shown no response to radiation, better results might be obtained by re-evaluating the case after radiation and considering radical sur-

gery. One third of the stage II cases showed no radiation response. This is certainly a group of cases in which the salvage rate might be appreciably increased by surgery. Some patients may require more radiation to bring about the desired effect, and these could be followed by means of vaginal smear to see if additional treatment would produce reaction in normal and malignant cells.

We feel that the study of the radiation response of cervical carcinoma by means of the vaginal smear represents a practical method which will aid in evaluating the effect of treatment on the tumor and will be a useful tool in the prognosis as well as the treatment of this disease.

SUMMARY

Seventy-three cases of cervical carcinoma have been studied by means of the vaginal smear during and immediately after radiation treatment for possible prognostic significance. They have been classified as good or poor responses. The prognostic accuracy is 88 per cent. The practical application of the method has been discussed.

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PATHOLOGICAL PHYSIOLOGY OF BILIARY DRAINAGE

The Use of a New Type of T-Tube and the Criteria for its Removal

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THE importance of exploring the common bile duct at the time of cholecystectomy and of subsequent T-tube drainage has been firmly established by many authorities. Prolonged T-tube drainage decompresses the biliary tree permitting recovery from cholangitis and pancreatitis. In addition to the therapeutic benefits, the T-tube affords a means for studying the pathologic physiology of the biliary and pancreatic systems. These studies are (1) roentgenological, (2) manometric, and (3) chemical. Roentgenologically one may detect the presence of hydrohepatosis, a missed stone, stricture, duodenal spasm, or pancreatitis. By pressure studies one is able to determine the degree of cholangitis, pancreatitis, ampulla edema, or spasm. By chemical tests of the T-tube bile one can determine the degree of liver damage present. By such means, therefore, the progress of recovery of the biliary system may be checked periodically and the exact time at which the T-tube should be removed can be determined. Previously, roentgenograms taken in the anteroposterior position have usually been considered adequate. We, however, have taken roentgenograms in the lateral position also, and have found to our surprise that the type of T-tube ordinarily used tends to pull out and a kinking of the common bile duct results. In some cases the common duct was so sharply kinked that obstruction to the flow of bile resulted. Accordingly, we have developed a new tube for biliary drainage which avoids kinking of the common duct. It is with the presentation of this tube and its comparison with the standard type that this paper is chiefly concerned.

A part of the work of this paper was done in Doctor Francis Henderson's Laboratory, fourth Surgical Service, Boston City Hospital, Boston, Mass.

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REVIEW OF LITERATURE

Lahey has written forcefully of the necessity for exploration of the common bile duct. In 1938 he reviewed his cases over a period of 28 years and showed that while the frequency of exploration increased from 15 to 50 per cent, the incidence of common duct calculi apparently increased from 8.4 to 18 per cent. In other words, the more he looked for stones the more he found. He also found that in 39 per cent of the cases in which common duct stones were found at operation there was no history of jaundice. An even higher incidence —up to 30 per cent of all of gall-bladder stone cases—of calculi in the common duct as well has been reported by others. Data published by Allen and by Walters have been confirmatory. Cutler and Zollinger (4) explored the common duct in 40 per cent of a series of cholecystectomy cases and found common duct calculi in 22 per cent. In a series of cases of choledocholithiasis reported by Judd, a history of intermittent colicky pain was found in 98 per cent, jaundice in 65 to 75 per cent. Bile was obtained on duodenal drainage in 83 per cent of these cases. These and many other surgeons have stated that there is little or no increase in mortality when choledochotomy is added to the cholecystectomy operation. Among present day indications for exploring the common bile duct may be listed the following: (1) a history of chills and jaundice; (2) palpable common duct calculus; (3) dilated common duct; (4) thickening of the head of the pancreas; (5) multiple small calculi or sand in the gall bladder when the cystic duct is large in size; (6) a history of calculi recovered from the stools.

While the necessity of common duct drainage has been generally accepted, the duration of the drainage has remained a matter of debate. There is no general agreement as to the proper length of time the T-tube should be left in place in any given type of case. Carter found on questioning 6 eminent authorities that there were no established criteria for the removal of the drainage tube. Opinion ranged from 2 weeks in uncomplicated cases to 2 months in cases showing marked cholangitis and evidence of marked obstruction at the time of operation. Few surgeons left the T-tube in for longer periods. Some believed that prolonged drainage predisposed to development of persistent biliary fistula or stricture of the common duct. Evidence is accumulating that these conditions very rarely occur in otherwise uncomplicated cases. In the cases which we have studied, we have found no evidence of any complications from the use of the T-tube. The biliary fistula healed promptly after removal of the T-tube in each case provided there was no stricture and the T-tube was not removed prematurely. Previously then, the optimum time for removal of the common duct T-tube has been a matter of personal experiences and opinion, therefore, a matter for debate. Within recent years we have developed certain physiological tests which we have found useful in determining the optimum time for the removal of the T-tube, and we have outlined these tests in previous communications (10, 12). They consist of roentgenologic and pressure studies for determination of patency of the common bile duct and the presence or absence of cholangitis. Briefly the T-tube is left in until the lower end of the common duct is patent and the cholangitis has completely subsided.

In the presence of obstruction preventing the normal emptying of the biliary tree, dilatation occurs throughout the entire system as demonstrated so clearly by Counseller and McIndoe, who have shown that the changes involved even the finest biliary radicals resulting in a diffuse process of "hydrohepatosis." In previous communications (10, 13), we have shown that these anatomical changes have their physiological counterpart as may be demonstrated by the disturbed intrabiliary pressure relationship. By means of a water manometer previously described (11), we have measured two types of pressure: (a) the resting intrabiliary and (b) the perfusion pain level. (a) The resting intrabiliary pressure, an index of patency of the lower end of the common bile duct, should be 30 millimeters of water or less. (b) The perfusion pain level, an index of common duct sensitivity and hence inflammation, is the lowest pressure at which the common duct can be perfused with saline before discomfort is experienced by the patient. A patient with a common duct free of inflammation can tolerate up to 500 millimeters of water without pain. When there is any obstruction to the flow of bile into the duodenum, the resting intrabiliary pressure will be found to be increased. If there is cholangitis present, the patient may experience pain on perfusion with pressures as low as 100 millimeters of water or less. Pressure readings are made 2 weeks postoperatively at which time the resting pressure is frequently found to be elevated and the pain level is often considerably decreased. As a result of the decompressing effect of continued T-tube drainage, these disturbed pressure relationships slowly change toward normal, unless the damage to the liver and ducts has been very severe. This return to normal values may not occur for a long period after relief of obstruction; even as long as 3 months or more.

The injection of a radiopaque substance by way of an inlying T-tube to obtain an exact representation of the contour of the biliary tree has been reported by Mirizzi and others. He reported a series of 400 cases collected over a period of 5 years. His method included the injection of lipiodol, at the time of operation, into some portion of the bile duct system for the purpose of obtaining an x-ray at once, "immediate cholangiography." Should an anatomical defect be found, Mirizzi explores the common duct. Robins and Hermanson reported 25 cases in which they had made use of this procedure at the operating table preferring hippuran because they found it less irritating. Other series of cases reported not only confirmed the value of this procedure as a determinant for or against common duct exploration, but also called attention to its

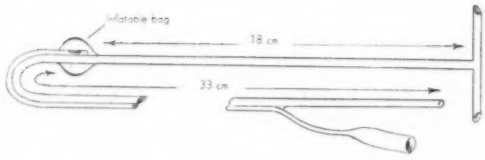

Fig. 1. A diagram of the new type of T-tube with attached Foley bag.

value postoperatively, the so-called delayed cholangiography. By these procedures it is possible to demonstrate and differentiate residual calculi, strictures, spasm of the duodenum, pancreatitis with swelling, malignancy of the bile ducts, ampulla of Vater or the head of the pancreas. The progress of the biliary tree in its return to normal caliber by decompression of the hydrohepatosis, by relief of obstruction and T-tube drainage may also be accurately followed. Various radiopaque substances including thorotrast, diodrast, brominol, lipiodol, hippuran, and skiodan have been used for cholangiography. We (11) have used skiodan, or diodrast, injection 15 to 25 cubic centimeters at body temperature into the T-tube, stopping the injection as soon as the patient notices a sense of fullness or distress. It is essential that no delay occurs in taking the x-ray picture after the injection. By use of this cholangiographic technique the beneficial effect of amyl nitrite or nitroglycerin in the relaxation of the smooth muscles of the sphincter mechanism of the biliary tract has been demonstrated (10, 11, 13).

Graham pointed out two decades ago that hepatitis is a constant accompaniment of cholecystitis. Snell has co-ordinated the degree of disturbance of liver function with the anatomical changes demonstrated at an operation. Gray, Nettrour, Bollman, and one of us (McGowan) (6, 7) have shown that in many cases of gall-bladder disease bile acid concentration was diminished in T-tube bile. The decrease of bile acids was found to parallel the degree of hepatic damage. In addition to the liver damage resulting from the biliary disease there was evidence of marked temporary inhibition of liver function as a result of conditions associated with the operative procedure. This temporary inhibition of liver function became progressively worse until the fourth to sixth postoperative day when the liver began to recover. In cases in which evidence of permanent liver damage was slight, recovery from temporary postoperative inhibition of liver function was rapid, a matter of days. In other cases in which there was evidence of marked permanent liver damage, the postoperative recovery of liver function was slow, in some cases requiring several months. It was found also that a moderately damaged liver does not completely regain its function of concentrating bile acids, a fact indicating a limit of repair after injury. This limit, judged from the bile acid concentration tests, appears to be reached usually at the end of the second week after operation, although improvement may be demonstrated for a longer period especially in cases of severe damage. This recovery was delayed by premature clamping of the T-tube. It was felt that T-tube drainage should be continued until the recovery of liver function had reached its maximum for that particular case; that is, until the bile acid concentrating power had ceased to improve.

METHOD OF STUDY

The T-tube described is the same as the standard type used except that an inflatable bag is attached approximately 18 centimeters from the cross limb of the "T" according to illustration in Figure 1. This bag is inflated by means of a second tube which is built into the first, the arrangement being similar to that used with the Foley tube.

Fourteen patients requiring drainage of the common bile duct were studied.

Criteria which we have used for exploration of the common duct were essentially the same as previously referred to. The common duct was opened longitudinally just below the cystic duct. The size of the incision made should not be greater in length than the diameter of the duct. The lower end of the common duct is usually gently dilated by means of a dilator or catheter. Forceful efforts at dilatation are avoided. Zollinger (18) has shown that forceful dilatation of the ampulla of Vater may result in postoperative edema followed by fibrosis and stricture.

The T-tube is inserted by the method shown in Figure 2. The bag is then inflated with sterile saline solution. Two weeks after operation the following tests are made: (1) pressure studies, (a) resting intrabiliary pressure and (b) perfusion pain level, and (2) roentgenogram of the biliary tract. Clamping of the tube is then started beginning with 1 hour twice daily. This period is gradually increased by a half hour twice daily until the tube is clamped off all the time. If the studies show elevated resting pressure or a low pain level, the clamping of the tube is delayed until pressure levels approach normal. After the T-tube has been clamped off continuously for 3 weeks it may be removed provided that: (1) the resting intrabiliary pressure is 30 millimeters of water or less; (2) the pain level is 500 millimeters of water or better; (3) the cholangiograms show absence of pancreatitis, stricture, or stone. By the technique and apparatus previously described (10, 11, 12) intrabiliary pressure studies were made starting on the 14th postoperative day in all cases reported. Fourteen cases were studied in all. The new type of T-tube was used in 6 cases and the standard type of tube in 8.

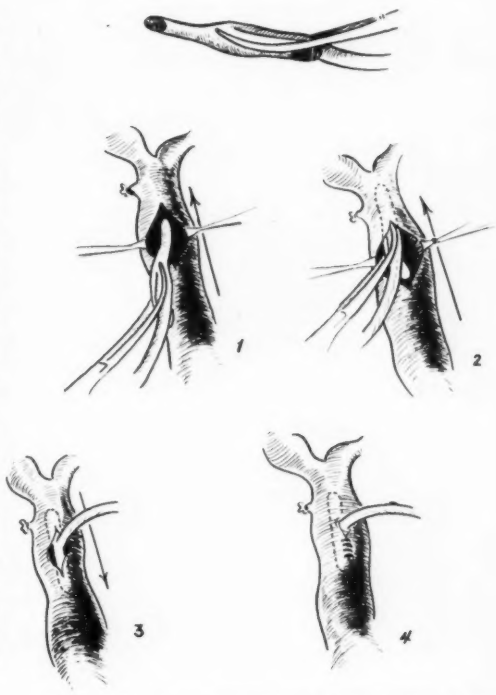

Fig. 2. This shows the method of introduction of the T-tube into the common bile duct. At the top is shown the manner in which the tube is grasped with a curved hemostat. *1*, The margin of the opening into the common duct is grasped on each side with Judd-Allis forceps. *2*, The T-tube is then introduced into the common duct and pushed upward toward the liver until the edge of the lower limb has past the margin of the opening in the duct. *3*, The cross-limb of the tube is then pushed toward the duodenum until the "T" is comp'eted. *4*, The defect in the common duct is then sutured on the duodenal side of the T-tube.

RESULTS

Of the 14 cases reported, stones were found in 6 (43%), pancreatitis in 1, and common duct pathology consisting of a stricture in 1 case. One showed a stricture of the ampulla of Vater with regurgitation of bile into the pancreas producing pancreatitis which secondarily produced more obstruction of the common duct and jaundice. Of the cases in which the old type of the T-tube was used, cholangiograms taken in the lateral position showed kinking of the common bile duct in each case (Figs. 3 and 4). This kinking varied from one of slight degree to one of a very acute type. In 1 case in which kinking of the common bile duct was extreme there was an elevation of the intrabiliary pressure. This pressure increased as the kinking became greater. The patient complained of considerable pain. The tube finally came out of its own accord in spite of all attempts to keep it in place by means of silk thread. In all cases in which the new type of T-tube was used roentgenograms showed slight or no kinking of the common bile duct (Fig. 5). In the patients drained with the old type tube there was a slight discharge around the tube due probably to continuous friction of movement between the abdominal wall and the tube. In the cases in which the new tube was used, the skin healed completely around the tube, and there was freedom from discharge or excessive granulations. In addition the intrabiliary pressure readings were in general lower than in the patients drained with the conventional tube. In 2 cases roentgenograms showed the presence of a small stone in the common duct which had escaped detection at the time of

a b

Fig. 3. *1*, Common bile duct; *2*, ampulla of Vater; *4*, hepatic duct; *6*, point at which common bile duct begins to tunnel the duodenum; the portion of the duct between *2* and *6* is intramural; *7*, T-tube. a, This cholangiogram taken in the lateral position shows the marked kinking of the duct by means of tension of the conventional type of T-tube. b, This is the same patient with a roentgenogram taken in the anteroposterior position; the usual position in which cholangiograms are taken. There is no evidence in this view of the marked kinking of the duct noted in the lateral view.

operation. In each case the stones were made to pass by applying the following procedure: the pressure apparatus was connected to the common bile duct and the perfusion pressure was slowly raised to 700 millimeters of water. The patient was given four deep inhalations of amyl nitrite. This procedure was repeated several times. Subsequent roentgenograms showed that the stones had passed. Of the patients in whom the standard type of T-tube drainage was used, 1 made a good recovery, 1 developed a pneumonia postoperatively, 1 made an uneventful convalescence, but was later admitted because of severe pain and died from pancreatitis and left ventricular failure. The remainder made an uneventful convalescence. In 1 patient with a stricture of the common bile duct which was drained by the standard tube the tube was pulled out gradually. In the cases of the new type of T-tube drainage, there were no postoperative complications. In those cases in which the T-tube was left in place until all the criteria referred to were satisfied, there have been no tendencies to fistula formation. On the contrary, the wound healed promptly, and in no case was there any biliary drainage after 24 hours. Further there has been freedom from late symptoms of biliary dyskinesia or the so-called postcholecystectomy syndrome.

DISCUSSION

Recurrence of symptoms after cholecystectomy are frequently reported. One of the reasons for this is due to the fact that the surgeon, while he may pay a great deal of attention to the gall bladder, often fails to realize that the biliary tract and the pancreas are frequently involved as part of the same disease. The cholecystectomy should be considered as only a part of the treatment, and prolonged biliary drainage should be performed when indicated. Drainage should be continued until the chemical, manometric, and roentgenological studies show maximum benefit has been obtained. The resting intrabiliary

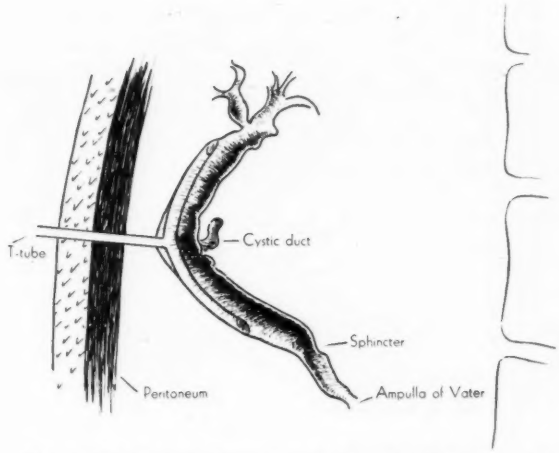

Fig. 4. This diagram, drawn to scale from the cholangiogram in Figure 3 shows the marked kinking of the common duct associated with the use of the standard type of T-tube.

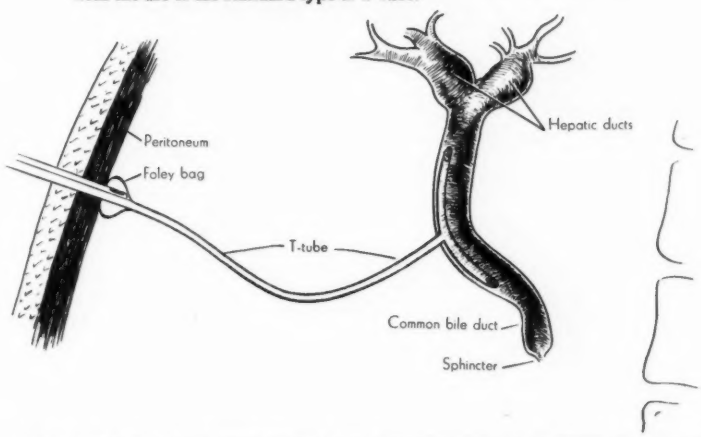

Fig. 5. This diagram, drawn to scale from a roentgenogram of an actual case, shows the new type of T-tube in place with no distortion of the common duct.

pressure determines the patency of lower ends of the common duct. The perfusion pain level is an index of the amount of inflammation within the biliary passages. It is really internal palpation. In external palpation we determine the degree of inflammation by applying pressure to the involved parts directly with the hand. In internal palpation of the biliary tract we use the amount of water pressure which the patient can stand as an index of the degree of inflammation in the duct.

SUMMARY

1. Cholecystectomy should be considered as only one phase of the treatment of a disease complex which may involve the gall bladder, bile ducts, liver, and pancreas at the same time. Exploration of the common bile duct should be performed in approximately 40 per cent of cases in which cholecystectomy is being performed.

2. Choledochotomy should always be followed by drainage of the common bile duct by

means of a T-tube. The T-tube is used for diagnostic and therapeutic purposes. Diagnostically, one is able to determine the presence of a missed calculus, cholangitis, pancreatitis, stricture, ampulla edema, or duodenal spasm. The diagnostic tests used are pressure studies, cholangiograms, and chemical analysis of the bile. Therapeutically, T-tube drainage is continued until cholangitis, pancreatitis, or ampulla edema has subsided. When T-tube drainage has been continued until maximum benefit has been obtained as indicated by prescribed tests, there has been no tendency for further symptoms to occur such as those which take place in cases of postcholecystectomy syndrome.

3. X-ray films taken in the lateral position have shown that the standard type of T-tube tends to be pulled out and a kinking of the common bile duct results. To prevent these undesirable complications a new type of T-tube with an attached inflatable bag is described. The benefits of this tube are: (1) absence of kinking of the common bile duct, (2) a clean wound with freedom from discharge, and (3) less tendency for the tube to be pulled out.

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CERTAIN PELVIC TUMORS ASSOCIATED WITH ASCITES AND HYDROTHORAX

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A DEFINITE clinical syndrome (Meigs' syndrome) consisting of ascites and hydrothorax associated with fibroma of the ovary has been recognized in recent years (2, 6, 11–14, 29, 31, 35, 51, 54, 56, 58). Certain other benign pelvic tumors may now be identified as causing this syndrome, which is of considerable importance because it presents a clinical picture usually associated with inoperable malignancy and pleural metastasis. In the group of lesions under consideration almost magical relief is afforded by surgical extirpation of the tumor.

ANTECEDENT STUDIES

The first recorded case of the syndrome, as it is recognized today, was reported by Cullingworth in 1879. His patient, a 36 year old widow, was found on physical examination to have two pelvic tumors, associated with ascites and bilateral pleural effusion. She died of cachexia, dyspnea, and general collapse. At necropsy the peritoneal and left pleural cavities were filled with fluid. Bilateral tumors of the ovaries were found; that on the right measured 12 by 9 by 5 centimeters and that on the left measured 15 by 12 by 7 centimeters. The pathologic diagnosis of the ovarian tumors was "bilateral fibromas with cystic degeneration."[1] In discussing his case, Cullingworth stressed the importance of the presence of ascitic and pleural effusion, inasmuch as up to that time it was thought that any tumor giving rise to such effusion had to be malignant. In 1892, Tait described the syndrome in an article entitled, "On the Occurrence of Pleural Effusion in Association with Disease of the Abdomen." He cited 2 cases. The first patient presented the typical features of malignant neoplasia with ascites and hydrothorax resulting from secondary deposits. The second, by contrast, was a 36 year old woman who had undergone repeated tapping for relief of ascites. At operation she was found to have a solid fibroma of the right ovary weighing 2 pounds, 2 ounces (about 1 kgm.). Tait remarked, "The lesson in this case is, in my opinion, a very valuable indication that no set of conditions in the abdomen, however apparently unfavourable, are sufficient to justify us in an absolutely unfavourable condemnation in any particular case."

Kelly and Cullen, in 1909, observed the combination of ascites and hydrothorax in a patient who had uterine leiomyomas. Satisfactory recovery followed hysterectomy. In 1914, Caro mentioned the occurrence of ascites and hydrothorax associated with a giant fibroma of the ovary. In 1923, Owen reported his own case of fibroma of the ovary associated with ascites, bringing out the fact that hydrothorax might complicate the aforementioned combination. Two of the patients in the 55 cases of fibroma of the ovary reported by Hoon in 1923 from the Mayo Clinic had bilateral hydrothorax as well as ascites. A single case of an ovarian tumor associated with ascites and hydrothorax was reported by Leo in 1926, but the type of the tumor was not revealed. Wong, in 1928, reported a case of ascites and hydrothorax associated with a twisted ovarian cyst. At operation the abdomen of the patient was found to be filled with blood-stained fluid. A large, hemorrhagic multilocular ovarian cyst, with two complete twists in its pedicle, was removed. The patient made a complete recovery.

Salmon, in 1934, reported 2 cases of benign pelvic tumors, each of which was associated

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[1] Coe, in 1882, observed the frequent occurrence of edema in the tumor substance of fibromas and cystofibromas of the ovary, and correlated the presence of edema with the formation of "geodes" or degenerative cysts.

with ascites and hydrothorax. One lesion was an ovarian fibroma; the other was a fibroid tumor of the uterus. In his book, *Tumors of the Female Pelvic Organs*, published in 1934, Meigs (33) described 3 cases from the Massachusetts General Hospital of benign ovarian fibromas associated with hydrothorax and ascites. In 1935 another case of fibroma of the ovary with pleural effusion and abdominal ascites, with complete cure after surgical removal, was reported from the records of the Massachusetts General Hospital (5). In 1937, Meigs and Cass published data concerning 7 cases of fibroma of the ovary associated with ascites and hydrothorax. These included the 4 cases from the Massachusetts General Hospital, Hoon's 2 cases from the Mayo Clinic, and Leo's case taken from the Italian literature. This was the classical report, defining Meigs' syndrome. In it the authors pointed out the possible coexistence of ascites and hydrothorax in the presence of benign fibroma of the ovary, and emphasized the importance of recognition of this association. Curability was now offered for a condition that formerly had been thought to have a basis in hopelessly inoperable malignant neoplasia. Rhoads and Terrell, in 1937, summarized 9 cases, taken from the literature, of ovarian fibroma with ascites and hydrothorax, and reported a single case of their own. They stressed the fact that this condition constituted a clinical entity, and suggested that it should be called a "syndrome." Weld reported 2 cases in 1938.

In 1939, Meigs (34) reviewed a total of 15 cases taken from the literature, including the original 7 contained in the report of 1937. Subsequent to 1939, reports of ovarian fibroma associated with ascites and hydrothorax have appeared in the literature with increasing frequency (2, 3, 9, 11, 12, 14, 17, 28, 35, 41). In 1943, Meigs, Armstrong, and Hamilton gave a synopsis of 27 cases of fibroma of the ovary in which evidence of signs or symptoms of fluid in the abdomen and thorax had been found. Healy, Herrick (16), Watson, and Taylor added 3 other cases in the discussion of the aforementioned synopsis.

Since 1940, other benign ovarian tumors associated with hydrothorax and ascites have been reported. Vogt noted a case of granulosa-cell tumor of the ovary associated with hemoperitoneum and hemothorax. Traut and Marchetti, in a study of 54 ovarian tumors of the theca-granulosa cell group, stated that in 1 case hydrothorax was a prominent symptom, and that at operation abdominal fluid had been found. MacFee reported a case in which a multilocular cystadenoma of the left ovary weighing 17 pounds (7.7 kgm.) was found to be associated with hydrothorax and ascites. Kelemen recently reported a case in which Meigs' syndrome had been caused by a Brenner tumor of the ovary. Perlmutter, and Mendel and Tyrone observed the same syndrome in cases of thecoma of the ovary. Rubin and associates reported a similar case. Millett and Shell recently reported a case in which pseudomucinous multilocular cystadenoma of the ovary was associated with hydroperitoneum and hydrothorax.

Meigs and his co-workers did not include either benign tumors (other than ovarian fibromas) or cancers in their reported series, but stated that when such lesions were found to constitute a large enough group they should be included in the syndrome. Benign tumors, as enumerated previously, now comprise a sizable group, and in some cases cancer also has been reported to be associated with the syndrome. Schenck and Eis reported a case of papillary cystadenocarcinoma of the ovary, and Anderson observed Meigs' syndrome in a patient who had a malignant cystadenoma of the ovary. Both of the patients in these latter 2 cases recovered after surgical removal of the tumors, indicating that the malignant nature of the tumors in itself was not the cause of the ascites and hydrothorax.

METHOD OF PRESENT STUDY

Records from the files of the Mayo Clinic from 1910 to 1945 were carefully examined for instances of pelvic tumor associated with ascites and hydrothorax (Meigs' syndrome). Nine examples of this condition were found among approximately 20,000 records of surgically removed pelvic tumors. An approximate classification of the lesions removed in these 20,000 cases is as follows: 16,000 uterine fibromyomas; 500 ovarian fibromas (this did not include all the smaller fibromas); 1,100

cystadenomas and teratomas; and 1,500 carcinomas of the ovary. This gives a total of 19,100. The rest of the tumors constituted a miscellaneous group which included granulosa-cell tumors and other lesions. The incidence of occurrence of this syndrome in this series was 0.05 per cent.

Pathologic material was secured. The tumors were studied in gross detail for pertinent data. Multiple blocks of tissue were then cut from the tumors and placed in a 10 per cent solution of fresh formalin. Sections were cut at a thickness of 10 microns on a freezing microtome and stained routinely with hematoxylin and eosin. The latter provided the material for the microscopic study.

In the present inquiry the 9 cases in question will be reported; then the clinical features will be considered; next the pathologic data will be analyzed; finally, the end-results of treatment will be presented, followed by comment on the condition in general, and by conclusions. The first 3 cases reported in the present paper also were reported by Hoon in 1923. The seventh case was reported by Masson and one of us (9) (Dockerty) in 1944.

REPORT OF CASES

CASE 1. A 36 year old married woman entered the clinic on July 3, 1917, complaining of "bloating" of the abdomen. Examination of the thorax revealed dullness and a decrease in fremitus, more marked on the left side. The abdomen was distended and a fluid wave was demonstrable; thoracentesis was performed once. A large mass was attached to the uterus. Roentgenologic examination of the thorax revealed the presence of fluid bilaterally. A large ovarian fibroma about 18 centimeters in diameter was removed surgically.

CASE 2. A 53 year old married woman entered the clinic on November 26, 1920, complaining of bloating of the abdomen and some degree of interscapular pain. Thoracentesis had been performed twice before she visited the clinic. There were physical signs of fluid in the right side of the thorax. This was confirmed by roentgenologic examination. Abdominal ascites was present. Thoracentesis was performed twice more before the patient was operated on. Surgical exploration revealed a large fibromyoma of the right ovary which weighed 510 grams.

CASE 3. A 59 year old married woman entered the clinic on September 19, 1929, complaining of progressive enlargement of the lower part of the abdomen of 1 year's duration. Physical examination revealed evidence of fluid in the left part of the thorax. A large pelvic tumor occupied the abdomen and extended to the umbilicus. Roentgenologic examination of the thorax showed the presence of fluid on the left side. Abdominal exploration disclosed considerable free fluid in the peritoneal cavity. A solid cystic ovarian fibroma measuring 19 by 10 by 8 centimeters was removed. The tumor weighed 835 grams. A section of it is seen in Figure 1.

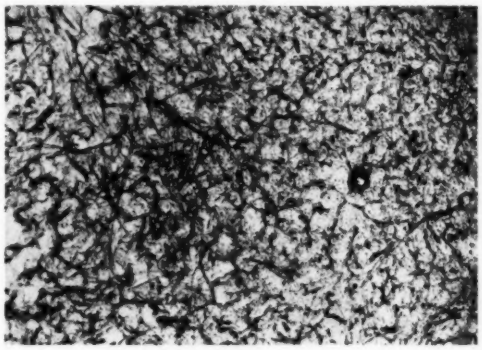

Fig. 1. Photomicrograph of a section of the ovarian fibroma in Case 3. Marked separation of the tumor cells by edema fluid is shown (hematoxylin and eosin ×60).

CASE 4. A 42 year old single woman entered the clinic on May 1, 1931, complaining of abdominal enlargement and a nonproductive cough of 6 months' duration. Signs of fluid were present in the lower part of the thorax on the right. The abdomen was large and distended. A fluid wave and shifting dullness were demonstrated. Abdominal paracentesis was performed; 13,000 cubic centimeters of clear straw-colored fluid was removed. Pelvic examination revealed an enlarged, freely movable uterus. Roentgenologic examinations of the thorax disclosed fluid in the right base. Surgical exploration revealed a large, degenerating fibromyoma of the uterus. This was removed. The uterus was not removed. The tumor was 12 centimeters in diameter.

CASE 5. A 49 year old single woman entered the hospital on March 27, 1933, complaining of dyspnea of 2 months' duration. Prior to this entry to the hospital, she had been hospitalized elsewhere for 3 weeks. Fluid was found in the right side of the thorax. Thoracentesis had been performed 4 times previously. Examination at the Mayo Clinic showed that fluid was still present in the right part of the thorax. The abdomen was markedly protuberant, and shifting dullness was demonstrated. Roentgenologic examination of the thorax showed pleural effusion to be present on the right side. Abdominal exploration revealed a large, degenerating tumor of the right ovary measuring 20 by 10 centimeters. Histopathologic examination demonstrated the lesion to be a mixed cylindroid and folliculoid type of granulosa-cell tumor of the right ovary.

CASE 6. A 50 year old married woman entered the clinic on April 26, 1940, with the report that a tumor

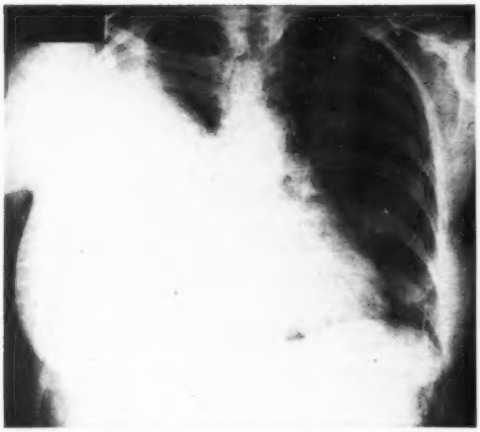

Fig. 2. Preoperative roentgenogram of the thorax of the patient in Case 7. The entire right lung, except for the apex, is obscured by fluid.

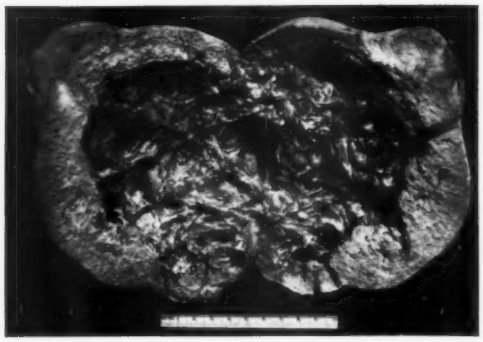

Fig. 3. Large ovarian fibroma removed from the patient in Case 7, showing a fibrous and edematous cut surface, with a large central cystic and necrotic region.

in the uterus had been discovered 4 months previously. Physical examination of the thorax revealed nothing abnormal, but roentgenologic examination disclosed fluid in the right base. Abdominopelvic examination showed a large, multilocular mass. Multiple uterine fibromyomas with diffuse pelvic inflammatory disease were found at exploration. A moderate amount of free fluid was found in the abdomen. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done.

CASE 7. A 43 year old married woman entered the clinic on November 11, 1943, complaining of dyspnea of 18 months' duration. Roentgenologic examination of the thorax in April, 1943, had revealed the presence of fluid on the right. Thoracentesis had been performed several times. Physical examination at the clinic disclosed signs of fluid in the right part of the thorax. This was confirmed by roentgenologic examination (Fig. 2). A large, firm, movable mass filled the suprapubic region of the abdomen. A fluid wave and shifting dullness were demonstrable. Thoracentesis was performed on the right. Surgical exploration was carried out, and a large fibroma of the left ovary, measuring 15 by 20 by 15 centimeters, was removed (Fig. 3). The tumor weighed 1,370 grams. A roentgenogram made 18 days postoperatively demonstrated a decrease in the amount of fluid in the thorax (Fig. 4). A roentgenogram made 15 months postoperatively showed that the fluid had disappeared completely (Fig. 5).

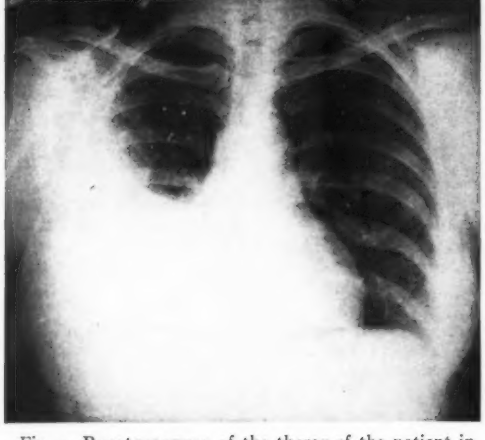

Fig. 4. Roentgenogram of the thorax of the patient in Case 7, made 18 days postoperatively, showing a decrease in the amount of fluid on the right.

Fig. 5. Roentgenogram of the thorax of the patient in Case 7, made 15 months postoperatively, showing complete disappearance of the fluid evident in Figure 2.

CASE 8. A 67 year old single woman entered the clinic on September 9, 1944, complaining of abdominal enlargement of 6 months' duration. Roentgenologic examination of the thorax showed fluid about the right base. The abdomen was enlarged, and a fluid wave and shifting dullness were demonstrated. A large pelvic tumor was noted. On abdominal exploration a large fibroma of the right ovary was removed. It measured 15 by 10 by 9 centimeters.

CASE 9. A 41 year old married woman entered the clinic on September 27, 1944, complaining of marked increase in the size of her abdomen during the preceding 2 months. Roentgenologic examination of the thorax showed that fluid possibly was present in the right base. The abdomen was large and distended. Shifting dullness was present. A mass was felt in the right lower quadrant of the abdomen. Surgical exploration was carried out. Marked ascites was found to be present. A complex teratoma and dermoid cyst of the right ovary were removed, together with the right fallopian tube, uterus and the left fallopian tube and ovary. The teratoma consisted, for the most part, of undifferentiated thyroid tissue.[1]

CLINICAL FEATURES

Age of patients. The average age of the 9 patients who had a pelvic tumor associated with ascites and hydrothorax was 48 years; the age of the youngest was 36 and the age of the oldest was 67 years. Both of these patients had ovarian fibromas.

Marriage and pregnancy. Six of the patients were married, and 3 were single. Of the married patients, 4 had given birth to 1 child or more, and 2 had no children. It was thus apparent that the parity of the patient had no relationship to the development of the syndrome.

Complaints. The most common symptom of which the patients complained at admission was enlargement of the abdomen. Some of the patients also noted the presence of a tumor mass. Abdominal bloating and shortness of breath were the next most common symptoms, and they occurred with about equal frequency. Pain was comparatively infrequent, usually arose from the lower part of the abdomen and was mild. Some patients had a cough, in association with dyspnea. The cough usually was nonproductive. The duration of symptoms had varied from 2 months to 5 years. The menstrual function of 4 patients was essentially normal; 3 patients had undergone the menopause; 1 had menorrhagia and 1 had metrorrhagia.

Physical examination. In nearly every case the triad "pelvic tumor, ascites and hydrothorax" was demonstrable by physical examination and roentgenograms or by roentgenograms alone. Ascites was noted clinically in all the cases. In several cases a pelvic tumor was not noted prior to operation, and in several other cases the presence of pleural effusion had not been suspected prior to the routine roentgenologic examination of the thorax.

Laboratory examination. Results of laboratory examination did not contribute any pertinent positive diagnostic information.

Diagnosis. The usual common causes for ascites presented a problem in differential diagnosis to the examiners of this group of patients. Cardiac disease, renal affections, cirrhosis of the liver, tuberculosis, and "malignant" peritonitis were some of the conditions which had to be distinguished from the true underlying pathologic process. Malignant neoplasm of the ovary, with ascites and

[1]While this paper was in the process of preparation, a tenth patient whose condition demonstrated the phenomena of Meigs' syndrome was seen. The following is an abstract of pertinent data.

A 71 year old white married woman entered the clinic on April 11, 1946, complaining of weakness and shortness of breath of 4 months' duration. During the previous 4 years the patient had noted some degree of dyspepsia and a slight increase in the size of her abdomen. On February 15, 1946, her local physician had discovered fluid in the right side of the thorax and since that date thoracentesis had been performed 9 times. She had lost 10 pounds (4.5 kgm.) since February, 1946. Physical examination revealed extensive pleural effusion on the right and a large pelvic tumor with questionable ascites. Roentgenologic examination of the thorax showed pleural effusion on the right side, with fluid extending up to the level of the third rib, anteriorly. On April 7, 1946, thoracentesis was performed on the right and 3,450 cubic centimeters of pale, amber-colored clear fluid was removed. The specific gravity of the fluid was 1.017. A cell count revealed no cells. Results of culture were negative. The protein count was 2.7 grams per 100 cubic centimeters of pleural fluid.

On April 21, 1946, 2 cubic centimeters of clear ascitic fluid was removed from the abdomen and 2 cubic centimeters of sterile India ink was injected into the peritoneal cavity. Two days later thoracentesis was again performed on the right and 2,000 cubic centimeters of smoky fluid containing India ink was removed, thus demonstrating the passage of fluid from the peritoneal cavity into the right pleural cavity. After thoracentesis, an abdominal exploratory operation was performed. A moderate amount of ascitic fluid was present. A large tumor about 10 centimeters in diameter was removed from the left ovary. A small fibrous-appearing tumor of the right ovary also was excised. Appendectomy was performed.

Pathologic examination of the tissues removed disclosed an edematous, degenerating, cystic fibroma of the left ovary measuring 10 by 7 by 7 centimeters. The tumor was attached to a small pedicle which apparently had undergone several twists. There was a fibroma of the right ovary 5 millimeters in diameter. The appendix showed chronic inflammation. Fluid from both the abdomen and thorax contained many pigment-laden cells. Study of the peritoneal coat of the appendix demonstrated similar phagocytosis by the lining mantle of mesothelium.

pleural metastasis, was the condition most often mistaken for a benign pelvic tumor associated with ascites and hydrothorax.

It is of historic interest to note that in Case 1 of the series reported herein the late Dr. W. J. Mayo in 1917 made the preoperative diagnosis of "fibroid" tumor of the ovary in a patient who had ascites and hydrothorax. At operation a large fibroma of the ovary was found. Since 1937, when Meigs' syndrome was recognized as an entity, only 2 patients who had fibroma of the ovary with ascites and hydrothorax have been seen at the Mayo Clinic. In both of these cases the preoperative diagnosis of Meigs' syndrome was made.

PATHOLOGIC DATA

Types of tumors. The lesions in the 9 cases reported herein consisted of 4 ovarian fibromas, 1 ovarian fibromyoma, 1 degenerating uterine fibromyoma, 1 fibromyoma of the uterus with pelvic inflammatory disease of the adnexae, 1 granulosa-cell tumor of the ovary, and 1 complex teratoma of the ovary.

Side of involvement. Five of the ovarian tumors were on the right side; 1 was on the left, and the location of 1 could not be determined on the basis of the data. Both the granulosa-cell tumor and the teratoma occurred on the right side. The 2 uterine fibromyomas were not localized as to side.

Size of tumor. All the tumors in this series were large. The average diameter was 16 centimeters.

Color of tumor. The ovarian fibromas were whitish or grayish white with a fine whorled appearance on cut section. The granulosa-cell tumor was grayish brown and was encapsulated.

Consistency. All the tumors were of the solid variety. Of the 5 ovarian fibromas, 3 were associated with cystic degeneration. Surface cysts were present on the granulosa-cell tumor. Gross edema was noted in every case of ovarian tumor in the series, and in 3 cases distention of the peripheral veins was present. In 3 of the cases adhesive tags were noted on the surface of the lesion.

Ascites and hydrothorax. Abdominal ascites accompanied the hydrothorax in all of the cases. Usually the fluid was considerable. In 7 of the cases pleural effusion was located on the right side; in 1 it was confined to the left pleural space; and in 1 it was bilateral. Performance of thoracentesis was necessary for 4 of the patients; 3 had undergone thoracentesis more than once. Abdominal paracentesis was performed for only 1 patient (Case 4), 13,000 cubic centimeters of clear straw-colored fluid being removed. At surgical exploration the amount of fluid varied from moderate to considerable amounts, as much as 3 to 4 gallons being removed from 1 patient. The fluid usually was described as being clear or straw colored. Diagnostic tests made upon fluid removed from the abdomen and thorax in these cases were of value only negatively; namely, in helping to rule out tuberculosis and malignant neoplasia.

Possible contributory factors to the occurrence of ascites may be mentioned in several of the individual cases. In the case of degenerating uterine fibromyoma (Case 4) the surgeon noted that a large fibroid tumor was incarcerated tightly in the pelvis, and thought that this might have accounted for the ascites. A similar situation was noted in 1 of the cases of fibroma of the ovary. In our case of pelvic inflammatory disease and of granulosa-cell tumor, twists in the pedicle were noted and were thought to have contributed to the production of ascites. Ascites frequently is an accompaniment of ovarian tumors which contain large amounts of thyroid tissue, as has been pointed out by Masson and Mueller. As previously mentioned, gross edema of the tumor or its pedicle or both was present in every case of ovarian tumor in the series.

Histopathologically, moderate to marked intercellular edema was noted in every case of the series, and it was particularly notable in the ovarian fibromas. In these there was marked separation of the tumor cells by the edema fluid; often associated with this were dilated blood vessels. Otherwise, the tumors exhibited no microscopic deviations from the picture seen in other similar tumors not associated with the syndrome under consideration.

END-RESULTS

All the patients made uneventful recoveries after surgical treatment and the end-results

were uniformly excellent. There was no recurrence of either ascites or hydrothorax in any of the patients. The longest follow-up period extended over 27 years.

COMMENT

The incidence of ovarian fibromas varies from 1 to 5 per cent of ovarian tumors, according to different authors. Masson and one of us (Dockerty) found that 312 of such tumors accounted for 5 per cent of all ovarian tumors surgically removed at the Mayo Clinic. The fibroma is one of the most common of the solid ovarian tumors. The comparatively frequent occurrence of ascites in association with ovarian fibromas has been recognized for some time, but the frequency of this occurrence has been variously reported. Peterson, in 82 cases collected from the literature, plus 2 of his own, found that the incidence was 40 per cent. Hoon noted that ascites was present in 25 per cent of 55 cases collected at the Mayo Clinic, and in a more recent report from the same institution, Masson and one of us (Dockerty) found that ascites accompanied 36 per cent of 141 fibromas the diameters of which exceeded 6 centimeters. Meigs and Cass reported the incidence of ascites to be 13 per cent in 29 cases of fibromas from the Massachusetts General Hospital.

Rubin and associates, in reviewing Miller's large collection of 2,748 ovarian tumors from various sources, found that ascites accompanied 6 per cent of the benign tumors and 45 per cent of the malignant tumors. The same authors noted that ascites had occurred in 30 per cent of their series of 23 theca-cell tumors of the ovary. In both Peterson's and Rubin's series, the amount of ascitic fluid was not proportional to the size of the tumor.

Origin of ascites. Since ascites generally is present in all forms of intraperitoneal carcinoma, the association of ascites with any pelvic tumor usually leads to the clinical impression that the tumor is malignant. In such cases the ascitic fluid is produced by chemical irritation of the peritoneum, which gives rise to a serous transudate and also to the secretion of malignant implants. The presence of the ascitic fluid in most of the cases of Meigs' syndrome, however, cannot be explained on the basis of chemical irritation of the peritoneum. Such attempts at explanation have proved entirely unsatisfactory.

Rather, a direct cause-and-effect relationship is involved, because removal of the tumor stops the formation of the abdominal fluid. Some have attempted to explain the origin of the ascites on the basis of Selye's alarm reaction (21, 48). The latter reaction is the response of the organism to an irritant (in this case, a pelvic tumor), with the production of a typical syndrome, the symptoms of which are independent of the nature of the damaging agent, and represent a response to damage as such. Among the responses is the production of pleural and peritoneal transudates. Selye regarded this stage as the expression of general alarm on the part of the organism, and termed it the "general alarm reaction." It might be compared to other general defense reactions, such as inflammation or the formation of immune bodies. After repeated insults by the irritant, the organism builds up resistance, and normal function returns. But after a period of months of continued trauma, the resistance disappears and there then appears a histamine toxicosis or anaphylactic shock, plus accumulations of peritoneal and pleural transudates.

The aforementioned hypothesis may be valid in certain experimental work, but it is not logical to explain Meigs' syndrome on the basis of such experimental observations. The pelvic tumor usually associated with ascites and hydrothorax is a fibroma of the ovary. That the mere presence of the ovarian fibroma in the peritoneal cavity is not a sufficient cause for the production of ascites is attested to by the fact that uterine myomas, despite their size, similarity in structure, and degenerative changes, cause ascites very rarely, although they are much more frequent in occurrence than are ovarian fibromas. Kelly and Cullen reported 5 such cases in which ascites undoubtedly had been caused by the presence of uterine myomatous tumors, and in 1 case pleural effusion was present as well. Salmon reported a similar case, and 1 case from the present series (Case 4) fits into this category.

Schenck and Eis offered an interesting hypothesis in explaining the production of

pleural effusion in such instances. They considered the presence of a pelvic tumor to be the initial factor; the tumor, by compressing the large abdominal lymphatic channels, retards the lymph flow through them. Schenck and Eis thought that when absorptive avenues through capillaries and lymph channels are abrogated, such as occurs in toxic damage to endothelium, increased permeability based on anaphylaxis and obstruction to the flow of lymph, fluid becomes trapped in large serous cavities and a vicious cycle results in ascites and pleural effusion, and, if this cycle is allowed to continue, subcutaneous edema. In reality, this explanation seems to be derived from Selye's alarm reaction plus the added factor of lymphatic obstruction by the compressing effect of the tumor. The fact that most of these tumors are large lends further credence to this theory.

As has been previously stated, there is insufficient evidence to explain the ascites on the basis of lack of protein in the blood. The number of serum protein determinations that have been found to be normal in this condition is insufficient to rule out such a condition as a cause. The ascitic fluid found in cases of pelvic tumor associated with ascites and hydrothorax varies in quantity from small amounts to 8 or 10 liters. In most cases, the fluid is clear and straw colored, and chemically appears to represent a transudate. In some instances it is blood tinged, and in such cases there is often evidence of recent twisting of the pedicle of the tumor.

One of the more recent and more nearly adequate explanations of the etiologic basis of the ascitic fluid is that offered by Masson and one of us (Dockerty), who, in a combined clinical and pathologic search for the etiologic "common denominator," found the following facts to be pertinent: Edema of the tumor or its pedicle or both was present in 31 of 51 cases of ovarian fibroma in which ascites was associated. This incidence of edema was twice that observed in the group of tumors not associated with ascites. Central cystic degeneration, with or without edema, frequently was noted in tumors of the "ascitic group," but was rare in the group of cases in which no free peritoneal fluid was observed at the time of operation. In 30 per cent of the cases in which there was ascites, adhesions, probably resulting from ancient twists of the pedicle of the tumor, also were present. Pain was an important clinical feature in this latter group. Small fibromas contained within the true pelvis were not productive of ascites.

Histopathologically, the aforementioned authors found that intercellular edema correlated more often than did gross edema and formation of cysts with the clinical production of ascites. Including the cases of edema with formation of cysts, separation of tumor cells by an excess of tissue fluid was observed in 70 of the 312 ovarian fibromas examined. Significant was the fact that of 51 tumors accompanied by ascites, 49 (96 per cent) exhibited edema, usually in marked degree. This was in contrast to an incidence of 10 per cent for edema in tumors not accompanied by ascites. In no instance was epithelium of a secretory type found on the surface of a fibroma where it might conceivably have given rise to ascites.

In connection with pathologic degeneration of the ovarian fibroma as a possible cause of ascites, Rubin and associates asked why ovarian fibromas produce ascites so commonly, whereas uterine fibroids do so rarely, even though both tumors have a similar parenchymatous histologic structure and undergo similar circulatory and degenerative changes. The explanation of Rubin and associates was found in the fact that uterine fibroids, are, as a rule, covered by a dense fibromuscular capsule and invariably by a serosal layer, whereas ovarian fibromas do not have such a capsule, and, like the normal ovary, have no peritoneal cover. Instead of a true serosa, ovarian fibromas are covered by a low, single-layered, very vulnerable and easily permeable surface mantle which offers practically no resistance to the penetration of fluid from the ovarian tumor. A more likely explanation may be that, for purely anatomic reasons, the ovarian vessels are more vulnerable to compression by a tumor mass or to twists in the pedicle than are the uterine vessels.

Origin of hydrothorax. To attempt to explain the origin of ascites when it accompanies certain pelvic tumors, notably ovarian fi-

bromas, presents a difficult problem in itself, but when there is added the concomitant occurrence of hydrothorax in some of these cases, the problem becomes even more perplexing. It is well to reiterate the direct cause-and-effect relationship mentioned in connection with ascites. That is, the failure of fluid to reaccumulate in either thorax or abdomen after removal of the tumor suggests that the tumor was responsible for the effusion. It has been pointed out that pleural effusion which accompanies ascites occurs more frequently on the right side than on the left. Meigs and Cass thought that lack of drainage of the right portion of the thorax by the azygos vein might explain this phenomenon, but later they did not believe this was an adequate explanation, inasmuch as the effusion also was found in the left part of the thorax and bilaterally. Borg reported a case of Meigs' syndrome with bilateral fibroma of the ovaries in which the patient died without the benefit of surgical treatment. At necropsy the azygos vein was found to be very large—being twice as wide as the abdominal aorta. It is difficult to evaluate to what extent the azygos system of venous drainage was interfered with, and just what role such interference might have played in the pathogenesis of the hydrothorax.

Lemon and Higgins and others (18, 19, 24, 26) have demonstrated experimentally the pathway by which lymphatic absorption of particulate matter proceeds through the diaphragm. They have shown that both surfaces of the diaphragm, with the exception of the tendinous center, are richly supplied with lymph vessels. Each half of the diaphragm forms its own separate area of lymphatic drainage and communicates but slightly with the other side. The lymphatic vessels on the right side are much larger and carry a greater proportion of the lymphatic flow than those on the left. Particulate matter is taken up diffusely on the subperitoneal surface of the diaphragm and passes between the mesothelial cells of the peritoneum into minute lymphatic vessels; from these minute vessels it passes to the muscle bundles until it is deposited in the subpleural lymphatic network. This transfer is rapid; it requires only 3 to 5 minutes in the normal muscle and 30 to 90 minutes in a paralyzed diaphragm. There are five main routes of communication between the peritoneal and pleural cavities. The first is the sternal route, which is the main channel and accounts for 80 per cent of the lymphatic drainage. It consists of three to four channels which course along the diaphragm between the intercostal muscles and proceed forward, parallel to the thoracic artery and vein. The second route is the pulmonary route, which extends to the nodes at the hilus of the lungs. The third is constituted by vessels which run to the thoracic duct. The fourth route consists of vessels which course over the dorsal surface of the diaphragm, pierce it, and empty into the lymph nodes in the region of the kidney. The fifth route is comprised by vessels that pass over the vault of the diaphragm, pierce it anterior to the aortic opening, then pass to the splenic mesentery and thence to the nodes in the region of the pancreas.

Lemon and his associates (25–27) have shown that fluids, as well as particulate matter and bacteria, are removed by the diaphragmatic lymphatic system in the transference from the subperitoneal to the subpleural lymph vessels, and they have demonstrated that this is a one-way communication. Although particulate matter injected into the abdomen of an animal reached the diaphragmatic lymphatic vessels, particulate matter injected into the thorax did not reach the inside of the abdomen. The direction of flow thus follows the direction of the normal current toward the heart. This is dependent mainly on the normal muscular contraction of the diaphragm. Florey, in his experimental work, noted that an intra-abdominal pressure of 3 to 5 centimeters of water was caused by the respiratory movements of the diaphragm. Intrathoracic pressure was negative to an almost equal degree. The difference in pressure on the two sides determines the direction of flow of the lymph.

The aforementioned work has demonstrated the passage of particulate matter through the diaphragm in the experimental laboratory. Yet, as Meigs and associates have pointed out, whether or not the material would be found in pleural effusion was not proved but only suggested, because the experimental animal has

no fluid in the thorax such as is present in pleural effusion.

Meigs and his co-workers deserve much credit for a fine clinical investigation of 2 patients who had Meigs' syndrome and who were operated on in 1941. These authors were able to examine the diaphragms of the 2 patients to collect fluids for analysis, and to demonstrate the passage of particulate matter from the abdominal fluid into the fluid in the thorax, in all probability through the diaphragmatic lymphatic vessels.

Ritvo reported a case of Meigs' syndrome in which peritoneoscopy was performed before the patient was operated on and in which air was left in the peritoneal cavity in an effort to demonstrate any passageway, if such existed, for air from the abdomen into the thorax. Roentgenograms were made immediately; these did not demonstrate that air found its way into the pleural space. On the basis of Meigs' and Ritvo's observations, then, it is unlikely that ascitic fluid reaches the pleural spaces by way of an opening through the diaphragm.

Rubin and his co-workers attempted to evaluate certain factors in the experimental production of Meigs' syndrome, and suggested several possibilities as to why ascitic fluid is not found in the pleura in every case of ascites. First, they wrote, the fluid entering the pleural cavity is absorbed rapidly, thus preventing accumulation of fluid in the pleural cavity. Second, the passage of fluid through the diaphragm is slow, so that the fluid is absorbed by the pleura with the same speed it takes to reach it. Third, the diaphragmatic stomas are blocked or obliterated by débris or chronic inflammatory changes of the peritoneum. Fourth, the high osmotic pressure of the colloidal ascitic fluid counteracts the transudation of water.

CONCLUSIONS

The association of ascites and hydrothorax with pelvic tumors was described in the older medical literature, but remained comparatively unknown to most of the medical profession until Meigs' classical report in 1937. The greatest credit is due Meigs for recognizing this syndrome and pointing out its clinical importance. A condition once thought to be an inoperable malignant process is now amenable to complete surgical cure. Meigs' syndrome originally was described as the coexistence of ascites and hydrothorax with benign fibroma of the ovary. Other pelvic tumors, however, both benign and malignant, should be included in the syndrome because they are being reported in the literature with increasing frequency.

Nine cases of pelvic tumor associated with ascites and hydrothorax were found in the records of the Mayo Clinic. In a tenth case the patient was seen at this clinic after the present paper had been completed. The 9 cases included 5 ovarian fibromas, 1 degenerating uterine fibromyoma, 1 fibromyoma of the uterus with pelvic inflammatory disease of the adnexae, 1 granulosa-cell tumor of the ovary, and 1 complex teratoma of the ovary. In the tenth case the lesions were ovarian fibromas. Pathologically, all the tumors were of the solid variety, and were large, averaging 16 centimeters in diameter. Gross edema of the tumor was noted in each of the 10 specimens. Microscopically, intercellular edema was noted in each tumor. It would seem that this edema can be correlated with the clinical production of ascites in each case. A large solid tumor can readily produce partial venous obstruction, edema, and in turn, ascites. Partial obstruction to the venous return also may result from twisting of a pedicle, inflammation, or adhesions. In 8 of the 10 cases, hydrothorax was situated on the right side. It was bilateral in 1 case and had occurred on the left side in 1 case. On the basis of the evidence reviewed, it appears that the fluid in the thorax results from the passage of ascitic fluid through the diaphragmatic lymphatic vessels.

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SURGICAL SUBSTITUTIONS FOR LOSSES OF THE EXTERNAL EAR

Simplified Local Flap Method of Reconstruction

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LOSSES of the external ear are numerous and often complicate other serious defects so that plans for rapid and simple restoration are important, without the use of massive distant flaps or great numbers of operations. The losses result mostly from burns, gunshot wounds, traffic accidents, and freezing. Congenital absence and loss from neoplasms account for a relatively small, but important number.

When enough surrounding scalp tissue is present, a fundamental plan can be used of freshening whatever is left of the stump of the ear and implanting it carefully under a scalp flap behind and above the ear. When union is firm (2 to 3 weeks) an adequate piece of costal cartilage is put in under the scalp flap, in the desired shape. In another 3 to 4 weeks, when there is no swelling, the flap and cartilage are dissected free of the skull so as to leave soft tissue attached to the under surface of the cartilage and to the skull. This procedure requires accurate, careful dissection. The resultant double raw surface is grafted with a single large thick split graft. Later adjustment may be necessary. If there is not adequate size, or the patient requests it, a small tubed flap from the immediate neck region can be added for the helix; this, however, is seldom requested.

With this simple plan, losses of the helix and pinna can be repaired in two operations, and total reconstructions of both ears have been done in as little as three operations (Fig. 1).

The patients in this series have been cared for in association with Major C. P. Scarborough, Captain Joseph Murray, Major Byron West, Lieutenant Allyn McDowell, Lieutenant Milton Edgerton, Major Shearburn, Lieutenant Jensen.

In making an ear, skin in front and behind is needed, with adequate support (or armature) in between. The scalp skin that was behind the ear is brought to the front surface of the ear, cartilage (preserved or fresh) forms the support, and a free graft goes in behind. It is recognized that a completely normal total ear cannot be made. There is no tissue available to make it with if it could be done. Although fresh (or preserved) ear cartilage may be used, or chips of costal cartilage may be molded into the exact shape, the skin available usually will not fit into the various recesses of the concha, triangular space, and curves of the helix to bring these variations of the cartilage into prominence. For these reasons, the restorations are recognized as substitutions, and size, general shape, and direction are concentrated on in total restorations, but a general outline and prominence may at least fail to attract notice. Many friends and surgeons have talked to the patient in Figure 1 without noticing that both external ears have been totally reconstructed.

Prosthetic ears of latex or soft plastic are used according to patients' wishes. They look like normal ears at a slight distance, but have the trouble of falling off and require more care than most patients want to give. (Their routine use would be acceptable to most surgeons.) What the patient wants is the deciding point.

The cartilage is a problem in many ways: of obtaining it, of shaping it, and of having it persist as a firm support. In Figures 1, 2, and 3, preserved costal cartilage has been used. A good supply is necessary and large

Fig. 1. Total loss from exposure to cold. Substitution done in 3 operations using local flap, single large piece of preserved cartilage and free split skin graft. Both ears in same condition repaired in same manner at same operations.

Fig. 1.

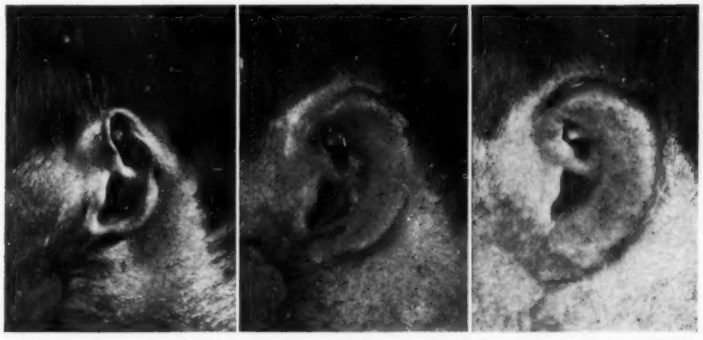

Fig. 1.

Fig. 2. Gunshot loss with occlusion of canal that had to be opened by using flaps of the available local tissue. Reconstruction done with neck flap brought up in stages, with preserved cartilage support.

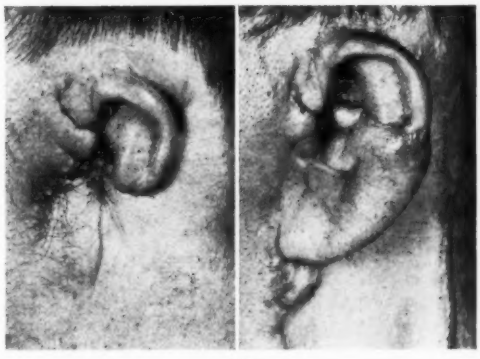

Fig. 2.

pieces, including the angle, have to be on hand to supply a large single piece for a full ear. When large numbers of patients have to be cared for the preserved cartilage is almost entirely relied on, and the opening of innumerable chests is avoided. The cartilage usually can be obtained from the pathology department of a large hospital, with proper selection of patients. It is thoroughly cleaned of all perichondrium and stored in merthiolate, alcohol, or other suitable chemical for use in the future.

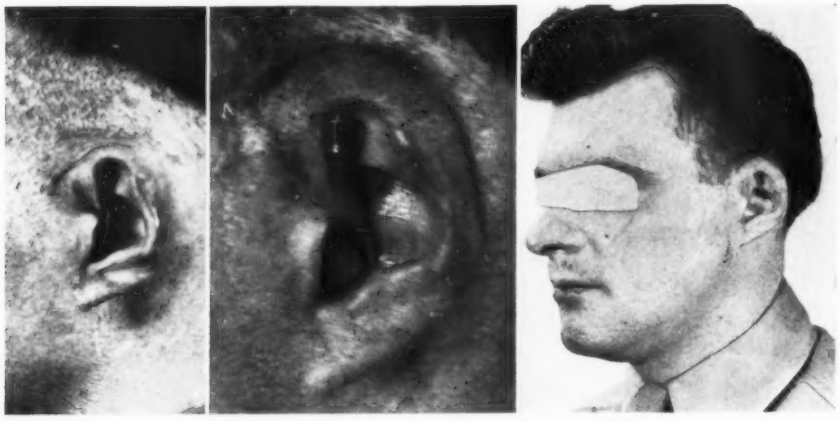

Fig. 3. Loss of about ⅓ of the bulk from fire. Reconstruction with local flap, preserved cartilage and split graft.

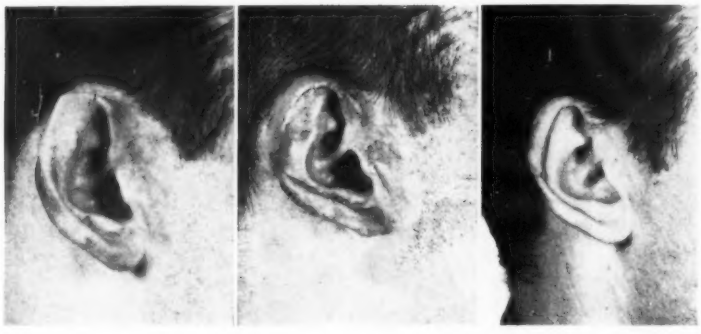

Fig. 4. Restoration crus of helix, pinna, helix with local flap and graft, 2 operations. Middle view shows ear implanted in scalp, no cartilage necessary.

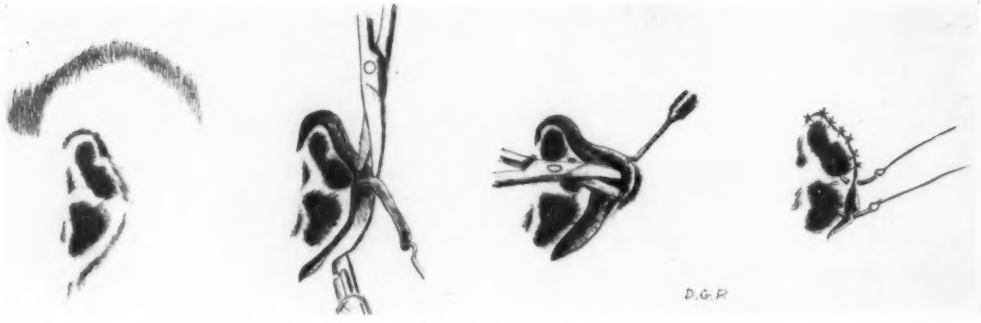

Fig. 5. Total reconstruction of auricle. The stump of the cartilage is opened by removal of edge scar. A flap of surrounding scalp tissue is raised and the stump is buried in under it. This is to give a blood supply to the flap from the front when it is raised later.

Fig. 6. After there is complete healing (3 weeks) an opening is made above and a complete tunnel made in the area. The curved portion of a costal cartilage is carefully carved to assimilate the normal contour and it is buried in the pocket.

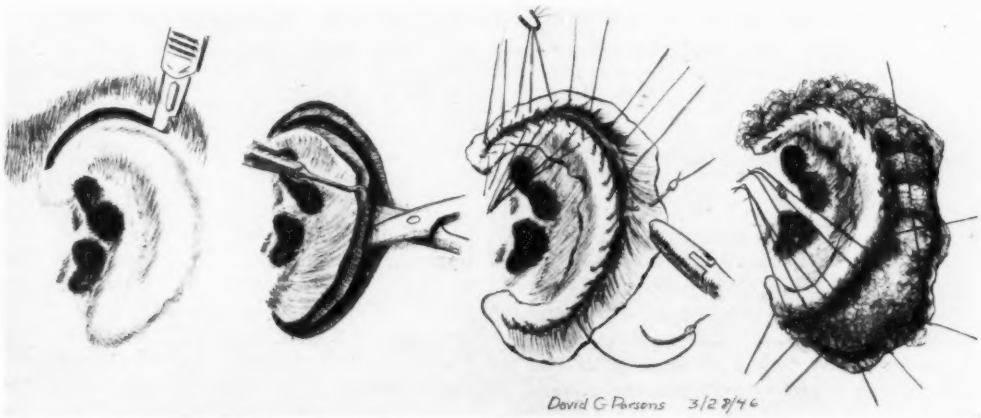

Fig. 7. After the cartilage is firmly in place, the ear is cut loose from the scalp with careful dissection to leave viable soft tissue on both the cartilage and the skull. The double surface defect is covered with a thick split graft as shown.

Carving of the cartilage is done in the operating room with no special equipment other than knives and a board. It is put in place through an incision above, into a pocket that is made with scissors. A good arm or strut is aimed down into the region of the crus of the helix to gain as much support as possible. Cartilage from other areas, such as the knee and septum and from animals has been tried, but for an active service using a large amount, a good source of fresh autopsy material is highly advisable. (That some other foreign substance may prove satisfactory is hoped.)

When the hairless skin around the ear is too limited, or is scarred and glazy, it may be necessary to do preliminary free grafting over the area, or to cut away just what hair is in the way and graft this area. Then the ear will be made out of grafts in these areas, the stages are necessarily slowed up, and greater care is necessary in the dissection.

When there has been avulsion of all local tissue as in gunshot wounds or traffic accidents, local flaps rather than free grafts may have to be supplied even to get started. Flap skin is thicker than the normal scalp in this

Fig. 8. The steps of two stage restoration of helix without necessity of cartilage. The edge is opened, a scalp flap is prepared, the ear remnant is planted under it at first operation. At the second operation the ear is cut loose from the scalp picking up the flap that was behind the ear to make the new helix. The resultant raw defects are grafted with a thick split graft.

area and, therefore, makes a bulkier ear. The flap may be brought up from the chest or neck. Figure 3 shows one that has been brought up in stages that has cartilage in it.

Ears that are crumpled from chondritis are very troublesome because of folds and uneven surfaces. If there is marked deformity of the cartilage, even though it is under good skin, consideration should be given the procedure of removing the deformed cartilage first and starting with as smooth a surface as possible. Trying to dig these lumps of cartilage out later is not very successful.

Partial losses, as of the helix and pinna, may not seem of much importance in comparison with other widespread destruction of tissue, but a thin, scarred, burned rim of the ear can be very uncomfortable for the patient. The repair of these defects is usually so simple and can be done so rapidly that there is little reason for not carrying out this partial reconstruction whenever requested.

The method is not routine for every patient, as there may be local shifts of small long flaps or forward dissections and replacements behind, but the fundamental, as stated, is to open the edge, prepare a direct flap, and either plant the ear under it or swing the flap into place. If cartilage is necessary, it is put in from the top, usually at a second operation; the ear is cut loose from the scalp and the defect is grafted at a subsequent operation. The patient in Figure 1 had total restoration in 3 operations with the use of cartilage. In the one in Figure 4 just the soft tissue without cartilage was used.

Sensation is usually slow in developing but little complaint is made. It is of course necessary to protect the patient against temperature extremes.

The use of composite free grafts from the opposite ear may be considered for small losses of the ear, and for restoration of the helix in total reconstructions.

RECONSTRUCTION OF THE ESOPHAGUS BY A SKIN-LINED TUBE

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LACK of esophageal continuity may be the result of congenital defect, trauma (usually chemical), or neoplasm. Improvement in anesthesia, chemotherapy, and thoracic surgical technique, has made it possible to save the lives of many individuals. Advances are particularly noteworthy in the group of infants with congenital tracheo-esophageal fistula, and in the carcinoma group. Survivors should be considered candidates for esophageal reconstruction.

Various practical considerations make it necessary to select cases carefully. Many infants are weak and sickly, and often, unfortunately, have other anomalies. Stenosis of the esophagus by lye presents a particular difficulty, because of the extensive scarring, especially at the upper end. This factor usually prevents deliverance of a patent upper portion of the esophagus to the skin surface of the neck. Carcinoma patients are usually older, and always undernourished. One is always concerned about local recurrence or remote metastasis.

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Even though life has been saved and nutrition improved, these patients still present a miserable picture. A gastrostomy is necessary, with all of its inconvenience, local irritation, leakage, and loss of gustatory satisfaction. In addition there is an upper esophageal fistula with copious salivary leakage, and if the leakage is prevented by stenosis at the cutaneous junction, saliva and food collect in the pharynx, causing discomfort and interference with respiration. It was the problem of relieving such a stricture at the skin surface that first caused us to consider the feasibility of reuniting the upper esophageal stump with the stomach.

CASE 1. J. I., a Puerto Rican widow, aged 70 years, first attended the clinic in June, 1937, because of hoarseness of 5 years' duration. A pedunculated fibroma of the hard palate and polyp of the vocal cords were removed. Blood count, urine, and stool examinations, Wassermann, chest x-ray films, and gastrointestinal series were normal, including the esophagus. On January 5, 1938, esophagoscopy was done to remove a piece of chicken bone lodged high on the anterior wall. In February, 1941, she first noted pain in the chest, and had difficulty swallowing anything but liquids. She returned to the clinic on April 21, 1941. Her health had been good since her

Fig. 1. Case 1. Front view, December 5, 1941. Side view, September 12, 1941.

Fig. 2. Case 1. January 5, 1942.

Fig. 3. Front and side views, Case 1, November 19, 1942.

last admission. Fluoroscopy showed a 4 centimeter symmetrical constriction in the middle of the esophagus. A biopsy specimen was taken from a mass arising from the posterior wall 27 centimeters from the upper gum. This tissue showed squamous carcinoma. Chest x-ray pictures were normal. On May 29, 1941, resection of the esophagus was done through the right 6th intercostal space by Dr. Allen O. Whipple and Dr. Richmond L. Moore. The lower esophageal stump was inverted and the upper end brought out through the right supraclavicular fossa and sutured to the skin of the chest. A gastrostomy was done. Microscopically, the tumor was poorly differentiated and involved muscularis. It measured 4.2 by 2.4 centimeters. The postoperative course was exceedingly smooth. Temperature was not elevated above 100.2 degrees. Sutures were removed on the 8th day. The patient was walking on the 9th day, and was discharged from the hospital on the 28th day. By August 15, 1941, the upper esophagus opening was entirely closed off, despite attempts to keep it open. This segment remained distended and the patient was uncomfortable (Fig. 1). On September 2, 1941, the esophageal fistula was re-established. Unfortunately, this fistula gradually became constricted. It was evident that a wide stoma was needed for the patient's comfort and was an essential step in any reconstruction. On December 16, 1941, the esophageal stump was freed and opened upward 2.5 centimeters., after which the skin and mucous membrane were sutured with interrupted No. 00000 plain catgut. Primary union was obtained.

Fig. 4. Case 1. Skin-lined tube opened posteriorly to show anastomosis with esophagus above and stomach below. Note V-shaped junction with gastric mucosa.

April 14, 1942, a skin-lined tube, 12 centimeters in diameter, was formed from the right infraclavicular region to the xiphoid. The patient was sent home on the 22nd day with the tube healed, but open at both ends. A strip of xeroform gauze was replaced in the tube at intervals of 2 to 3 days. The patient continued to gain weight and there was no irritation of the skin within the tube.

August 6, 1942, the lower part of the skin tube was extended down over the xiphoid and anastomosed to the anterior wall of the stomach. A 4 millimeter white nodule on the peritoneal surface of the stomach proved to be a leiomyoma. The patient's recovery was smooth. Her highest temperature was 100 degrees F. The wound healed primarily, and sutures were removed on the 7th day. On the 13th day a glass connecting tube was used to link the upper end of the skin tube with the esophageal opening (a distance of 5 cm.), and the patient was allowed to drink a glass of water. The passage was free. The patient noted a sensation of coldness. Checked

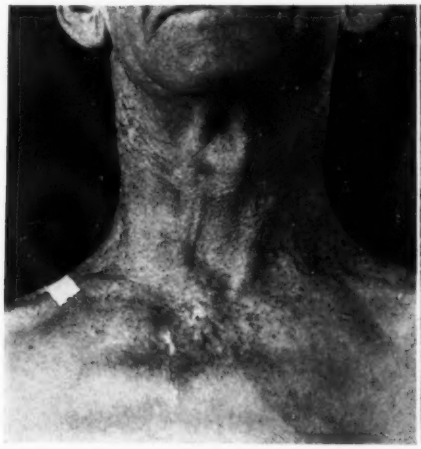

Fig. 5. Case 2. April 21, 1942.

Fig. 6. Case 2. May 1, 1942.

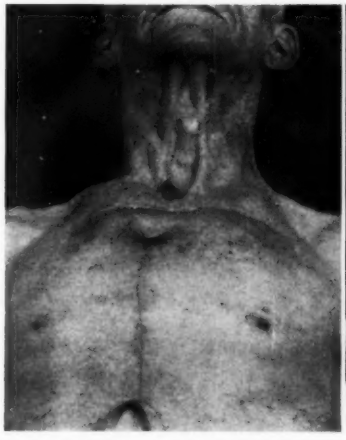

Fig. 7. Case 2. November 25, 1942.

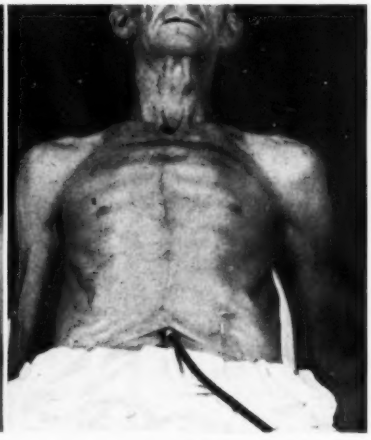

Fig. 8. Case 2. March 8, 1943.

fluoroscopically, the lumen of the skin tube appeared larger than that of a normal esophagus. There was occasional pyloric obstruction due to the mushroom gastrostomy tube, and this caused regurgitation of strongly acid stomach content. It was noted that this regurgitated material irritated the exposed skin, but not the skin lining the tube. Under local novocain anesthesia the skin tube was continued upward and joined to the esophagus. Healing was uncomplicated and 10 days later the patient was allowed to eat and swallow. Food passed freely down the tube. The gastrostomy tube was withdrawn and the stoma promptly healed. The patient began to regain strength and weight.

September 2, 1942, 17 months after esophagostomy the patient developed pneumonitis with signs of consolidation at the left base, and a temperature of 103 degrees F. She was flushed and coughing. A week later there was effusion in the left chest and mediastinal shift to the left, indicating atelectasis. After aspiration of cloudy yellow fluid, showing negative cultures, and no tumor cells, x-ray examination showed a wide mediastinal shadow which continued to enlarge, and the patient became more cachetic. She died March 19, 1943. Autopsy showed carcinoma in the tracheobronchial lymph nodes, with extension to the posterior mediastinum, and occlusion of the left main bronchus. The skin

Fig. 9. Front and right side views, Case 2. January 10, 1946.

lining of the tube was smooth and clear. Scarring was not noticeable, and there was no evidence of ulceration anywhere. The tube consisted of skin, averaging 10 centimeters in circumference, with no evidence of surrounding scar. A scarcely distinguishable suture line ran down the tube anteriorly. The juncture of the skin-lined tube with the stomach showed no scarring or ulceration, and the epidermis showed an abrupt transition to the normal gastric mucosa. The anterior wall of the stomach was adherent only at the site of anastomosis and at the obliterated gastrostomy.

CASE 2. W. R., a 61 year old man, complained of dysphagia for 3 months before his admission on November 19, 1941. He had lost 40 pounds in weight, and had had trouble swallowing fluids. Chest x-ray pictures were normal, except for calcified bronchial nodes. Barium studies showed esophageal obstruction just below the arch of the aorta. Esophagoscopy showed a tumor 33 centimeters from the upper teeth. Biopsy proved squamous carcinoma. Blood count normal; erythrocyte sedimentation reaction 8 millimeters, Wassermann negative; weight 150 pounds. Histamine test showed no free hydrochloric acid; total acid 9 after 40 minutes.

December 19, 1941, esophagectomy was performed by Dr. Allen O. Whipple assisted by Dr. Richmond L. Moore. A right transthoracic approach through the 7th intercostal space was used. The pleura was found adherent and so was the esophagus in the region of the calcified nodes. It was necessary to excise the left vagus nerve with the mass. The upper esophageal stump was brought out just to the right of the suprasternal notch and a gastrostomy was made. The portion of the esophagus examined pathologically was 9 centimeters long and had a con-

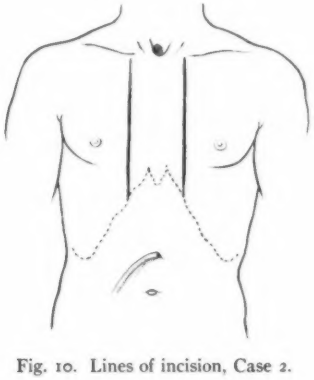

Fig. 10. Lines of incision, Case 2.

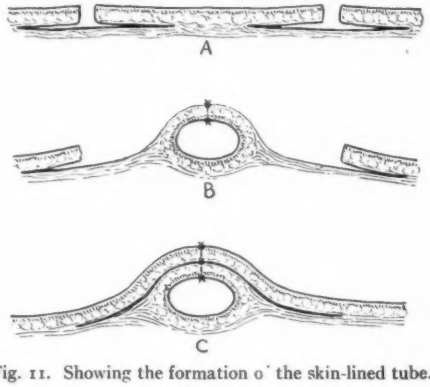

Fig. 11. Showing the formation of the skin-lined tube.

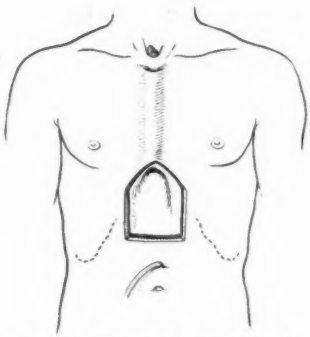

Fig. 12. First step in extending tube.

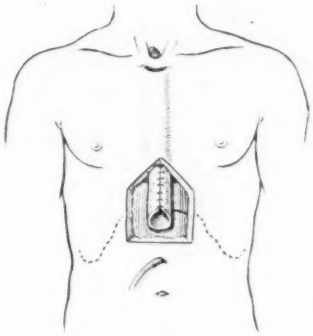

Fig. 13.

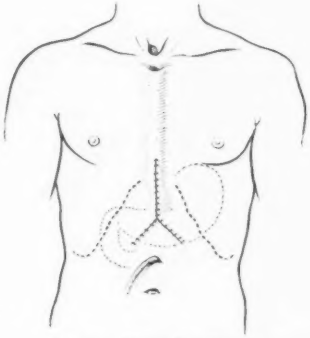

Fig. 15. Wounds sutured.

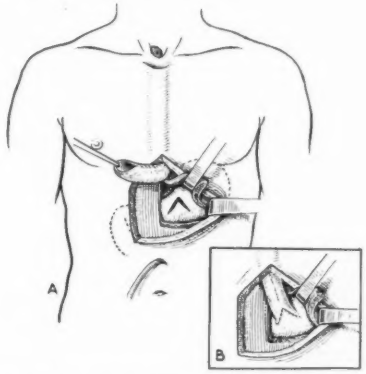

Fig. 14. Exposure of stomach and V incision; inset shows tube sutured to stomach.

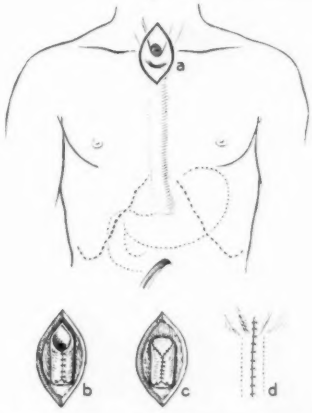

Fig. 16. Elliptical incision has been made to join esophagus and skin tube. Insets show methods of closure.

stricting area of carcinoma 2.5 centimeters long. There was muscle invasion, and mitosis averaged two per high powered field. The mucous membrane was much more extensively involved than was grossly recognizable. The postoperative course was stormy for 3 days because of bilateral pneumonitis. Temperature mounted to 105 degrees F., but settled to normal by the 7th day. The wounds healed well, and the patient was discharged, on gastrostomy feedings, on January 19, 1942, weighing 135 pounds. Upon readmission on April 20, 1942, the esophageal stoma was closed by a dense scar. This scar was excised and the stoma was enlarged (Figs. 5 and 6).

September 3, 1942, there was no constriction so a cutaneous tube 9 centimeters in diameter was formed from the sternal notch to the xiphoid. This was followed by union of the lower end to the anterior wall of the stomach (Figs. 7 and 8).

December 1, 1942, wound healing was uncomplicated and sutures were removed on the 9th day. Patient was discharged home on the 18th day.

March 9, 1943, the skin tube and esophagus were united without complication. The patient started swallowing water on the 6th day, and soft diet was started on the 10th day. He has had no obstruction and has required no treatment. He became interested in having his teeth repaired, "in order to do some chewing again," and resumed his work as a sheet metal worker in a war plant. His weight has been maintained at 150 pounds.

January 11, 1946, he was in good condition. His only untoward sensation is a strong perception of heat or cold on ingested food and fluids, and in the morning an itching sensation which he relieves with a cup of strong coffee (Fig. 9).

OPERATIVE TECHNIQUE

Stage 1. *Formation of subcutaneous skin-lined tube.* Two parallel incisions are made from just below the esophageal stoma to the xiphoid. In the first case these were 12 centimeters apart, and in the second 9 centimeters. Eight centimeters may be enough. Incisions

were made to include the deep fascia, and the lateral margins were widely undermined, about 10 centimeters. The medial margins are freed about one-third, leaving the central third attached down the center (Figs. 10 and 11). The central layer is then rolled up, skin surface in, and sutures with two layers of interrupted No. 000 chromic catgut. The inner layer is tied with the knot inside the lumen, and the outer layer in the fascia. The undermined lateral flaps are then closed over the tube in two layers, No. 000 interrupted chromic gut sutures being used in the fascia, and interrupted dermal in the skin. A roll of xeroform gauze is passed down the tube. When this strip of gauze is changed every 2 days, a fresh piece may be tied to the old one, and pulled through as the old one is removed.

Stage 2. Anastomosis to stomach (Figs. 12, 13, 14, and 15). The tube is extended by continuing the two parallel cuts down almost to the gastrostomy which is carefully draped out of the operative field. The lowest 2 centimeters of the tube is left open. The anterior wall of the stomach is exposed through the left rectus and an inverted V incision is made into the stomach. Each branch of the V is 4 centimeters long. The skin of the tube is then sutured to the gastric mucosa with interrupted No. 000 chromic gut reinforced by a second layer of similar sutures between the fascia of the tube, and the gastric serosa and muscularis. The linea alba needs a small vertical incision to the xiphoid to insure against angulation of the tube. Then the wound is closed, and the undermined skin is approximated. At this stage the gastrostomy needs to be kept open on bottle drainage most of the time, because gastric content regurgitates freely up the tube and will excoriate the skin of the chest; strangely enough, however, the skin of the closed tube can be seen to remain clear. Perhaps, drying or oxidation is needed to activate the irritative process.

Stage 3. Junction of esophagus and skin tube (Fig. 16).

An elliptical incision is made vertically, including the upper end of the original parallel cuts. The skin tube is then closed up to the esophageal stoma, and the upper end of the ellipse turned down in the manner of an envelope flap to close the upper angle of the wound. The undermined skin margins are then closed. Liquid feedings in small amounts may be started as soon as the skin is healed.

SUMMARY

Loss of esophageal continuity may result from congenital defect, trauma, or neoplasm. Improving surgical technique permits survival of an increasing number of patients, and this leads to consideration of a means of reconstruction. Two cases are presented with a description of the method used to unite the upper esophageal segment to the stomach by means of a skin-lined tube.

SOME OBSERVATIONS ON WOUND HEALING

A Clinical Study, with a Note on Topical Chemotherapy and Secondary Closure

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THOMAS B. JONES, M.D., Rochester, New York

THIS report is concerned with the management of wounds in a general hospital based in the United Kingdom and actively engaged in the treatment of wounded evacuated from the continent. Shortly after D-Day, it was necessary to outline a plan whereby a large number of wounds could be treated definitively. Whereas everyone was well versed in the emergency treatment of wounds, there was less agreement and precedent as to the definitive treatment. There were those who strongly advocated that all extensive soft tissue wounds with and without fractures be treated according to the principles popularized by Orr and Trueta, while others postulated that in certain instances secondary closure and grafting might be utilized in the definitive treatment of open wounds after varying lengths of time. There was little agreement as to the rôle of local and systemic chemotherapeutic agents. Much information had been disseminated concerning arbitrary time intervals after which débridement and closure might be hazardous or inadvisable. Therefore, it seemed that an excellent opportunity was at hand to make some observations upon the factors involved in wound healing.

Methods of study. Approximately 6,000 patients were admitted to the surgical service in the 6 months after D-Day. Between 2,000 and 2,500 wounds were secondarily closed. This is a report on approximately 725 that were treated on the general surgery section. The results have been carefully tabulated and provide the basis for this report.

The following plan was adopted. It was decided to make an earnest effort to close every wound either by secondary suture and/or graft as soon as it was reasonably certain that the wound was not the site of active virulent infection. The closure of the wound was made the primary objective and the underlying fracture, nerve injury, foreign body, tendon injuries, or muscle defect, when present, were a secondary consideration. This policy was predicated on the premise that the best dressing for any wound is skin, and the sooner it is applied the better is the ultimate prognosis of the associated injury.

Time interval. All wounds were closed as soon as possible. Some of the wounds were closed within 3 or 4 days, and many were closed during the first week. The majority were sutured or grafted between 7 and 14 days. It was believed that if the patient had not developed clinical evidence of local or systemic infection within 48 to 72 hours after the emergency treatment had been carried out there was little reason to continue open treatment of the wound in the anticipation of infection that did not exist. It soon became apparent that the earlier the wounds were closed the better were the results.

Early management after reception. All wounds were dressed as soon as possible after admission. Vaseline packs were removed. Many of the large wounds had been enclosed in plaster casts, often with admonitions against their removal. These were likewise promptly removed. A simple wet saline dressing was applied to all wounds in order to remove the caked sulfa crystals, vaseline, exudate, and old blood. It was remarkable to see the striking improvement in the appearance of these wounds after 24 to 48 hours. All medication (sulfadiazine and penicillin) was stopped after admission, and subsequently given only in those cases in which there were systemic signs of infection. In one group of 100 patients, it was necessary to give chemotherapy in only 2 instances when

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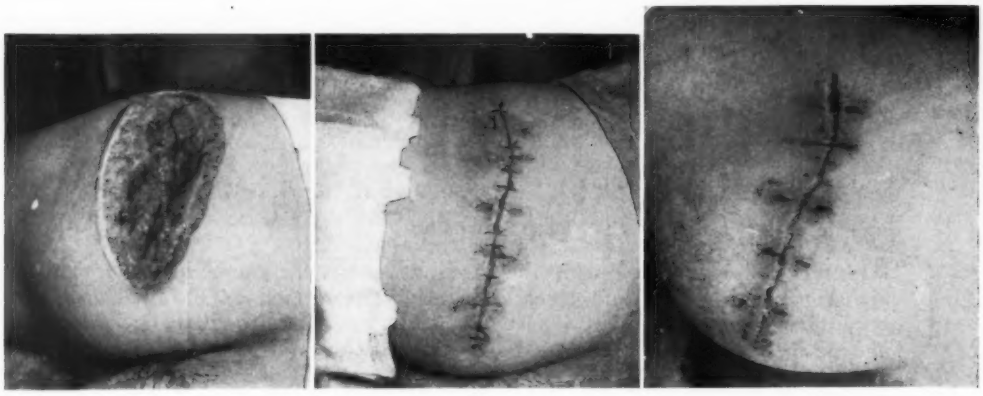


a b c

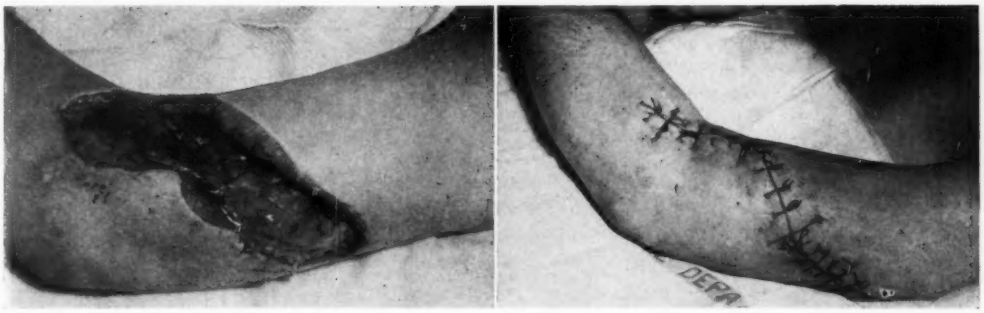
Fig. 1. Wound of buttocks, 7 days after injury. a, Large defect with divided gluteal muscles. There is minimum granulation tissue and this type of wound may be closed without redébridement. b, Illustrates wound 7 days after closure with through-and-through mattress sutures of black silk. c, Wound at 14 days.

these indications were followed. The simple saline dressings were changed frequently in order to utilize the absorptive and capillary action of the gauze. Each time the gauze was removed and reapplied gross foreign matter was mechanically removed from the wound. Maximum benefit from the wet dressings was usually obtained in 2 or 3 days. As soon as it was felt that the wound was reasonably free of all gross particulate and organic matter, closure of graft was done.

Technique of closure. The skin was carefully prepared with soap, alcohol, ether, and a mercurial antiseptic. The wound was protected during this procedure with sterile gauze. The local anesthetic, when used, was introduced circumferentially into the normal skin and was not put directly into the wound. Early wounds (less than 7 days old) were simply sutured together with little undercutting, redébridement seldom being necessary. These wounds did not have granulation tissue, were still mobile, and gave some of our very best results. Black silk sutures were used and only in exceptional instances were buried sutures used. When there was difficulty in obliterating dead space a large pressure dressing was put over the wound. Drains were practically never used. When large muscle groups had been interrupted it was often possible to approximate them by the use of figure-of-eight black silk sutures which traversed the skin and were subsequently removed.

Older wounds (10 days and longer) were handled in a different manner. Simple closure over granulation tissue and its fibrous base invariably gives an unsatisfactory result. The wound by this time has lost a great deal of its mobility and closure of even minor defects is difficult without rather extensive undercutting of the wound edges. Therefore, small granulating wounds, whenever possible, were completely excised in the same manner that one would excise a nevus or skin carcinoma. An elliptical incision was made in the normal skin about the wound, and the granulating area with its base removed by sharp dissection so that the wound then possessed the appearance of a fresh one. Meticulous hemostasis was observed and the wound accurately closed without drainage. This operation of secondary débridement is of prime importance when dealing with granulating wounds. Wounds have healed exceptionally well when closed in this manner and rather unsatisfactorily when simple closure was attempted without excision of the granulation tissue and fibrous base.

Large skin defects oftentimes made closure impossible. These were closed by a combination of partial suture and split thickness graft. Secondary débridement operations were consistently carried out, and the skin edges were



a b

Fig. 2. Soft tissue wound of elbow, 3 days after injury, 2 days after débridement. a, Appearance of the wound after 24 hours of saline dressings. b, On 9th postoperative day simulates healing seen in clean operative wounds.

mobilized and sutured from the periphery inward to render the defect as small as possible. A thin split thickness graft was then immediately sutured into the remaining defect over any exposed muscle, fascia, bone, tendon, or nerves. On the thighs and legs some of these defects were enormous, and the areas grafted in some instances extended from the buttocks to the knee. A successful take is almost invariably obtained when the graft is placed over these redébrided wounds, and in our experience the results are far superior to those obtained when grafts are placed over granulating surfaces.

Oral sulfadiazine (6 gm. per day) was begun on the day before operation and continued for 4 or 5 days after operation to protect against an occasional spreading cellulitis. From the beginning we made a hard and fast rule that chemotherapeutic agents would not be used locally in the wound. Penicillin was employed neither systemically nor topically. We felt that if we were properly to evaluate the results it was of prime importance for all personnel to adhere rigidly to a well standardized procedure. It was originally planned to operate upon 50 patients with this technique for purposes of establishing a control. We were already convinced that chemotherapeutic agents used locally were of little value when the wound was ready for closure, and it was felt that in some instances the presence of these agents was even harmful and a deterrent to wound healing. From the beginning the results were out of all proportion to our anticipations, and this policy was therefore followed in 600 consecutive cases. In an additional 125 cases, a mixture of penicillin and sulfanilamide was dusted into the wound at the time of closure.

On the other hand, on some of the other sections of the surgical service, notably orthopedics, various types of topically applied agents were used freely. Some of the wounds were irrigated postoperatively with penicillin through tubes introduced into the wounds at the time of closure. Others had sulfanilamide alone and some were dusted with a mixture of sulfanilamide and penicillin. These wounds were followed closely; the results did not offer any convincing evidence that the local application of these chemotherapeutic agents offers any advantages, and the practice was eventually discontinued.

Foreign bodies. Insofar as possible foreign bodies were made a secondary consideration and wounds were frequently closed over tiny bits of shrapnel in inaccessible depths of the wound with no apparent interference in healing. After the wound was healed and if the foreign body was responsible for any symptoms, it was removed at a clean operation. This undertaking was thought to be preferable to one which would allow extensive dissections in a contaminated wound. Large foreign bodies, however, when they carry in segments of clothing, must be removed. The cultures from these retained pieces of clothing frequently yield Clostridium welchii, when there is no clinical evidence of gas bacillus infection.

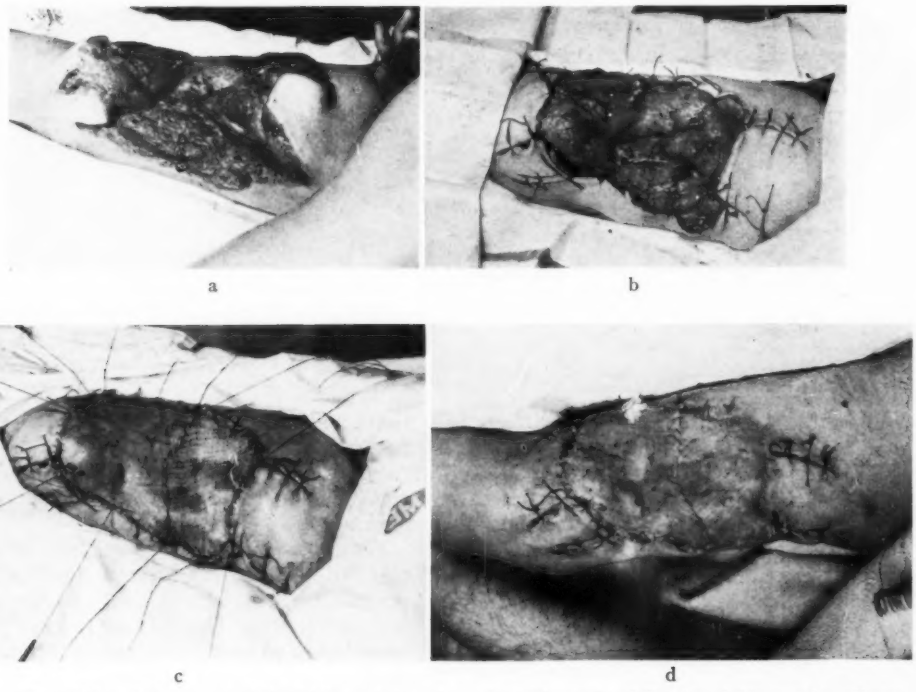


Fig. 3. Wound of posterior aspect of the thigh, 13 days after injury. a, Illustrates deep muscle defect with exposure of femoral artery, sciatic nerve and femur. b, Illustrates initial step in reconstructive surgery. The wound has been completely redébrided and a partial closure accomplished by undercutting and mobilization of skin margins; all granulation has been excised. c, A large split thickness graft was applied immediately as a dressing for the remaining defect. d, Appearance of wound 8 days after operation. There is a complete take of the graft.

Foreign bodies, 1 centimeter or over in diameter, almost invariably have to be removed because of the cloth which has been carried in.

Results. The results were tabulated in three arbitrary categories. Group I included those that healed primarily without drainage. They usually required little or no dressing after 7 days and simulated the healing of clean operative wounds. Group II included those which exhibited "wet healing." In this group there was usually some reaction about the sutures and frequently serosanguineous drainage. However, the Group II wounds were well healed in 14 to 16 days and did not require any further definitive treatment and were considered to give just as satisfactory an end-result as those in Group I. Groups I and II comprise the "satisfactory" group. Group III included those closures considered unsatisfactory because at the end of 2 weeks they were not healed and frequently required additional surgical procedures, such as grafting, suture or strapping, to obtain final epithelization of the wound.

In 600 patients who did not receive topical chemotherapy, primary healing (Group I) was obtained in 67 per cent of all wounds closed. Wet healing (Group II) was obtained in 29.3 per cent. Unsatisfactory results (Group III) were obtained in 3.7 per cent of the cases. With this technique of wound closure, 96 per cent of the cases (Group I and II) can be placed in the "satisfactory" group.

In 125 patients with "dusted" penicillin and sulfanilamide, there was no significant difference in the total of "satisfactory" results (95.6 per cent). However, there was an increased incidence in the "wet-healing" group (35.6 per cent), and a somewhat lower per

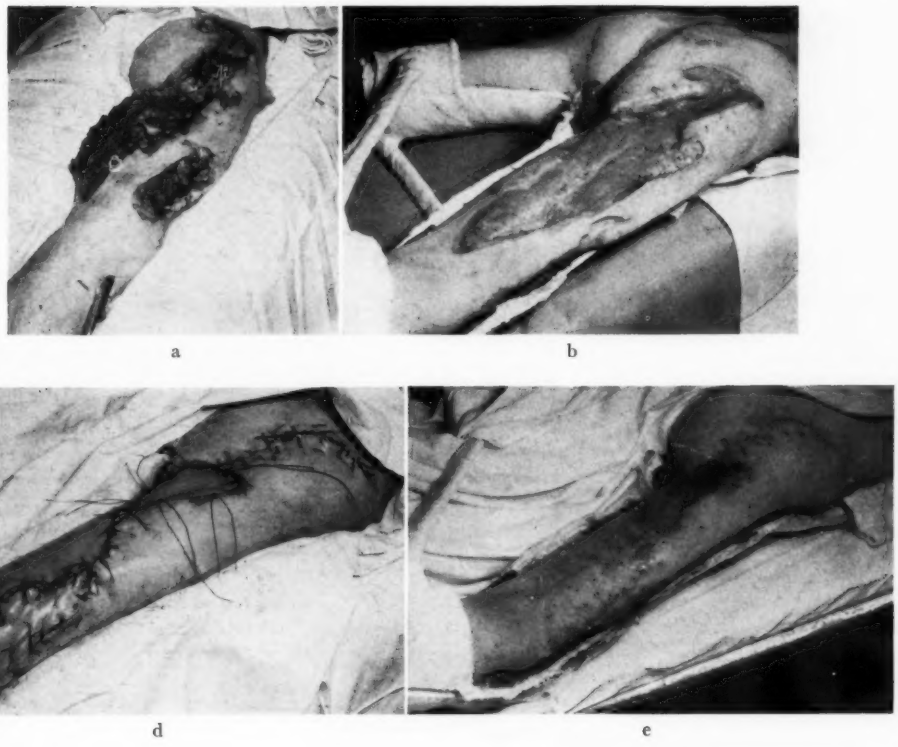


Fig. 4. Compound fracture of the femur with extensive soft tissue injury. a, Illustrates appearance of the wound 6 days after injury. There are large masses of necrotic muscle and fascia. Débridement has been incomplete. b, Illustrates the wound 3 weeks after the redébridement. c, X-ray film. d, After closure and graft. e, Wound completely healed.

centage in Group I (60 per cent). Unsatisfactory results occurred in 4.4 per cent of the cases.

When first confronted with several hundred large contaminated wounds of the buttocks, arms, legs, and trunk, it is not without some apprehension that one undertakes closure. It can be candidly stated, however, that in only a few instances throughout the entire series were signs of systemic infection observed following secondary suture. The most amazing defects could frequently be drawn together with considerable tension and primary healing would still occur.

CASE REPORTS

CASE 1. *Extensive wound of the buttock:* This soldier was wounded June 14, 1944, by a high explosive shell. Thorough débridement was carried out in Normandy, France. The wound was initially dressed with vaseline gauze and local sulfanilamide. Penicillin was not given in any form. He was given an indeterminate amount of sulfadiazine orally. He was admitted to the hospital June 20, 1944. Vaseline packs were removed and wet saline dressings applied on the 20th and 21st of June. The soldier was then

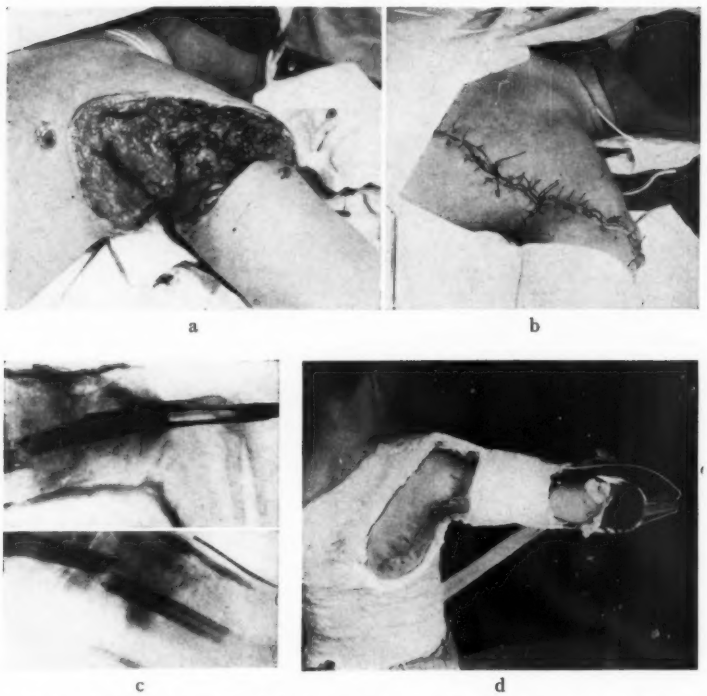


Fig. 5. Compound fracture of the humerus. a, Ten days after injury. b, After re-débridement and closure. c, X-ray films. d, Two weeks after suture.

taken to the operating room and the wound closed under local anesthesia (1 week after injury). The wound was 5 or 6 inches in depth and the gluteal muscles were completely divided. Closure was accomplished with deep through-and-through silk sutures which included the margins of the divided muscle. No local chemotherapeutic agent was placed in the wound. The wound was closed under considerable tension as can be seen from the illustration (Fig. 1a) and the suture line was reinforced with strips of adhesive. A large pressure dressing was applied. Figure 1b shows the result at 1 week. No medication was given during the postoperative period except oral sulfadiazine for 5 days. At the end of 2 weeks the patient was up and about and the wound was completely dry and perfectly healed.

CASE 2. *Extensive wound of the elbow:* This soldier sustained a penetrating wound of the forearm near the elbow from a machine gun bullet on June 23, 1944. Débridement was not done until the following day at which time the wound was packed with vaseline gauze and sulfanilamide powder. He did not receive penicillin in any form. He was admitted on June 25, 1944. The vaseline pack was removed, wet dressings were applied for 24 hours and closure was done on June 26, 1944 (2 days after original débridement). No local chemotherapy was given. Sulfadiazine was given orally on the day preceding operation and for 4 days after operation. Complete primary healing was obtained. Physical therapy was begun 14 days after operation.[1]

CASE 3. *Massive wound of posterior aspect of thigh:* This soldier was wounded on July 25, 1944 by an aerial bomb. There was extensive hemorrhage and shock, and débridement was not done until 48 hours following injury. He was evacuated to the United Kingdom and arrived in Oxford August 2, 1944 (5 days after primary débridement). He was in a plaster of paris hip spica and his field medical record contained the following note: "Recommend: Cast not to be removed for a minimum period of 8 weeks because of massive tissue loss. Femoral artery, femur and sciatic nerve exposed at time of operation for a distance of 6 inches." There was a nauseating odor and much drainage through the cast, and it was therefore promptly removed. The wound involved the

[1]Primary healing is almost invariably observed in wounds which are closed with a few days of the primary débridement. Most of the complications in wound healing after secondary closure were observed in those wounds which were much older. This suggests that sutures might well be placed in the wound at the original operation and after 2 or 5 days, if inspection reveals the wound to be clean, the wound can be closed by simply drawing up the sutures (delayed primary suture).

entire thigh and was swathed in vaseline gauze. There was much purulent exudate in spite of the fact that he had received large doses of penicillin both at the field hospital in France (initial intravenous dose of 100,000 units) and during his transport to the United Kingdom.

A large simple saline dressing was applied and changed frequently during a period of 4 days, and on August 7, 1944, he was taken to the operating room and a partial closure accomplished by mobilization of the skin margins (Fig. 3b). Granulations were just beginning to appear and they were removed from the muscle surfaces. The femoral vessels were exposed for a distance of 5 or 6 inches in the depth of the wound and the femur was covered only with a thin fascial layer. A single sheet of split thickness skin was taken from the opposite thigh with a free hand-knife and sutured into place in the remaining defect (Fig. 3c). A large pressure dressing was applied. Figure 3d illustrated the appearance of the wound at the first dressing with a complete take of the graft. Physical therapy was begun in about 10 days and the patient was out of bed on the 14 day with the wound healed. Penicillin was not used. Nothing was put into the wound topically and the only medication was sulfadiazine orally.[1]

CASE 4. *Severe compound fracture of the femur:* This soldier sustained multiple shrapnel wounds of the right thigh and abdomen, and a compound comminuted fracture of the femoral shaft, also an intracapsular fracture of the neck of the femur, on June 16, 1944 in Normandy. A partial débridement was done about 4 hours later. Eviscerated loops of bowel were replaced within the abdomen, a portion of omentum resected and the abdominal wound closed. In the following 48 hours he received 15 units of plasma, 20,000 units of penicillin every 4 hours, two transfusions of whole blood and sulfa drugs topically and systemically. He was admitted to our general hospital 4 days after injury in very poor condition: temperature 101, pulse 120, hemoglobin 45, red blood count 1.9 million, and white blood count 28,000. He was in a hip spica which was soaked with blood. He was given several blood transfusions in the following 48 hours and then taken to the operating room where the cast was bivalved. Figure 4 illustrates the condition of the wound June 22, 1944, (6 days after the original injury) and it can be noted that there had been incomplete débridement. There was much necrotic tissue which was removed from the wound. A Kirschner wire was inserted into the tibial tuberosity for traction. A new double hip spica was applied. On July 6 the cast was bivalved and the wound treated extensively with saline dressings which were changed frequently in preparation for closure of the wound. On July 16 (1 month after wounding) the patient was taken to the operating room and the wounds were completely closed by secondary suture and split thickness graft (Figure 4b illustrates the appearance of the wound after wet saline dressings and secondary débridement and Figure 4d shows the wound immediately after secondary closure. Figure 4e shows the wound completely healed just before he was sent to the United States with a simple fracture of the femur in good position.

This case is an excellent example of how a severely wounded man with multiple injuries has gone through the various steps in the chain of evacuation to make a good recovery. It is our feeling that these compound fractures, no matter how severe, can be converted into simple fractures in many instances when good surgical principles are observed. On the other hand these extremely large wounds would take months to heal by secondary intention and when packed with gauze and kept open, there is opportunity for infection of bone, secondary hemorrhage, and disability from scar contracture. (This patient was treated in collaboration with Lieutenant Colonel Yancey, Chief of the Orthopedic Section and Major C. N. Mell, Assistant Chief of the Orthopedic Section.)[1]

CASE 5. *Compound fracture of the humerus:* This soldier was wounded in the right shoulder by a high explosive shell on September 1, 1944. There was severe hemorrhage and shock. He was treated in a field hospital ½ hour later, and débridement was done followed by the application of a shoulder spica. Penicillin was not used. He was given oral sulfadiazine in adequate amounts. He was admitted to this hospital 8 days after injury (September 9) and on September 11 he was taken to the operating room and the wound was closed without topical chemotherapy. Secondary débridement with complete revision of the wound was performed and he was given several transfusions for his anemia. (Figure 5 illustrates the appearance of the wound before and after closure and again 2 weeks later.) This is another example of how a very extensive compound fracture can be converted into a simple fracture by simple closure. This procedure is only possible because of the skillful débridement. He had a completely healed wound only 3 weeks after injury whereas the plaster treatment of such an open wound would result in purulent drainage and prolonged convalescence. There is also evidence to support the view that healing of bone is greatly enhanced when the wound is covered with skin. (This case was under the care of

[1]This is a gratifying result and is much better than many weeks or months in a plaster cast. There likewise is complete restoration of function without limitation of motion by scar which is an invariable sequel of prolonged healing by secondary intention. The presence or absence of a fracture in the involved bone should not make the slightest difference in the basic principles involved in the healing of the wound. We consistently treated fractures of the femur with extensive soft tissue loss in the same manner. There is no question but that compound fractures left open with large vaseline packs over a period of many weeks, invariably develop a certain degree of bone infection whereas, if the overlying wounds are promptly closed, a compound fracture, in the great majority of cases, is converted into a simple fracture and infection avoided or minimized. This should prove to be one of the most significant contributions of the war, and differs radically from the original precepts popularized by Orr and Trueta.

[1]A survey of 100 consecutive compound fractures of the femur treated by secondary closure revealed that 92 per cent of them healed completely and were returned to the United States 62.9 days after hospitalization; 95 cases showed evidence of bony union. This series of cases will serve as the basis for a subsequent report by Lieutenant Colonel Daniel L. Yancey, Chief of Orthopedic Section.

Lieutenant Colonel D. L. Yancey, Chief of Orthopedic Section and Major C. N. Mell, Assistant Chief of Orthopedic Section.)

Analysis of results. It has been surprising to observe that 96 per cent of so called contaminated wounds heal satisfactorily when closed by secondary suture. The policy of leaving traumatic wounds open after careful débridement and the rôle of systemic chemotherapy in the prevention of hemolytic infections no longer needs to be defended. However, there is less agreement as to the management of these same wounds after they have once reached a general hospital where definitive treatment may be carried out. Medical curricula have rather universally included strict admonitions against the closure of contaminated wounds after some arbitrary time interval. Once this interval had expired, it was thought necessary to keep these wounds open for an indefinite period of time in order to avoid infection which presumably would follow closure. The present experience shows this reasoning to be invalid. This is in contrast to experience reported in the last war. Several factors must be considered as a possible explanation for the excellent results that were obtained. In the beginning, the excellence and promptness of emergency treatment rendered cannot be minimized. There are two outstanding features in connection with essential primary treatment—good surgical débridement and the transfusion of whole blood. Experience in this war has demonstrated that there is no substitute for the latter under battle conditions.

Penicillin. The antibacterial potency of penicillin is well known. Many of the wounded had received penicillin both topically and systemically, beginning at the forward area and continued through the echelons of evacuation. It was given on the LST's at regular intervals when the patients were brought across the channel, as well as on air evacuation ambulances enroute to the United Kingdom. It is extremely difficult to accurately evaluate the effect that this prophylactic measure has had upon the subsequent absence of infection when these wounds were closed. We are inclined to minimize the effect that it has had upon the bacterial flora of the wound, however. For example some of our sickest patients had received penicillin in adequate amounts but arrived extremely septic because of retained clothing or necrotic tissue in the depths of a wound. It was invariably true that when débridement had been inadequate, penicillin had little or no effect, and it was also true that when débridement had been adequately done, it seemed to make little difference whether penicillin had been given or not. We admitted many patients who had had only 1 or 2 doses of 20,000 units over a period of several days. Their field medical records still carried a notation "penicillin treated" and in the subsequent analysis of results, such cases give an unreliable index of the efficacy of penicillin. Many patients had received none whatsoever and their subsequent course, when definitive treatment was carried out, varied little or none from those in which large amounts of penicillin had been given. There were many patients who received a large initial intravenous dose at the time of débridement in France but did not receive a single dose thereafter. Their records are still classified as "penicillin treated" and are misleading in this respect. It was rare to encounter a patient who had received therapeutic doses of penicillin at regular intervals and one must be extremely critical when evaluating the rôle that this drug played. Our cases did not receive penicillin either preoperatively or postoperatively except for definite indications. Wherever possible efforts were then made to identify the organism and its sensitivity.

A nearby general hospital on the other hand has used penicillin extensively as a prophylactic measure. During the month of July 1944, this neighboring hospital used 2,208,000,000 units, while in our work during the same period we used 9,500,000 units. In other words, in treating approximately the same number of patients with the same type of wounds, the neighboring hospital used 200 to 250 times the amount of penicillin that was used in our hospital. A few cases on the orthopedic service with compound fractures received penicillin irrigations to the open wounds. This practice was discontinued because there was little difference observed when these wounds were

compared with others that were treated with ordinary wet dressings.

Penicillin remains extremely valuable in the armamentarium of the war surgeon where definite indications exist for its use. It does seem, however, that there is considerable evidence in the present study to show that its routine prophylactic use is of equivocal value and perhaps wasteful. In the great majority of cases there is no such indication and in this series satisfactory healing was observed in 96 per cent of the cases without the use of penicillin.

Sulfonamide therapy. Much of the conflicting evidence in both experimental and clinical studies on wound healing is a result of a failure adequately to control conditions. We determined from the beginning to treat all wounds uniformly so that there would subsequently be an opportunity to evaluate the results. There seemed to be considerable evidence to support the view that the local use of the sulfonamide drugs in contaminated wounds possessed many limitations. The inhibitory powers of the para-amino benzoic acid derivative are well known and the wounds with which we were dealing invariably contained a certain amount of purulent exudate. In addition the relative insolubility of the various drugs results in an exudation of plasma like fluid into the wound which in many instances is detrimental to wound healing. Ten grams of sulfa drug in a wound will frequently give a blood level of only 2 or 3 milligrams per cent and this is not of therapeutic value. For example, erysipeloid infections in the periphery of open wounds do not respond well to local sulfa drug medication when it is used alone but they promptly subside on adequate dosages by mouth. It was decided that if an indication for a sulfa drug existed it would be given in adequate dosages by mouth.

As is well known, the majority of wounds when they occur on the battle front are dusted with sulfanilamide powder before the first aid dressing is applied. In addition most of them are subsequently treated locally at the time of secondary dressings and almost invariably at the time of débridement. The soldiers also take 4 grams by mouth at the time they are wounded in most instances and the oral medication is almost invariably continued. Intravenous sulfa drugs have also been utilized freely at forward medical stations. There is no question but that this has been of tremendous prophylactic value and there is no doubt but that it is the reason that streptococcus cellulitis rarely occurred in the wounded of this war. Septicemia as a complication is extremely rare.

The inclusion of this potent bacteriostatic agent in the armamentarium of the war surgeon has allowed a freedom of action which has permitted many advances in the surgical treatment of these contaminated wounds. One of the single factors which has allowed surgeons to close compound fractures and large soft tissue defects—oftentimes many days after the original wound—is the security afforded by the knowledge that one possesses an agent which successfully combats hemolytic infection and prevents septicemia.

All of the patients in this series received sulfadiazine before and after wound closure. In several hundred cases there was not a single case of systemic infection. In only a few instances was it necessary to open a wound to liberate pus. An occasional wound showing an area of cellulitis would invariably subside on wet dressings and subsequently heal primarily. As evidence accumulated there was little to condone the topical application of chemotherapeutic agents. They are capable of interfering with healing because they act as foreign bodies, they increase the exudation of fluid into the wound and the therapeutic value has never been unequivocally proved.

It should be re-emphasized that whenever débridement had been inadequate in the emergency treatment of the wound, there were frequently dire consequences, no matter how adequately the various chemotherapeutic agents had been administered either topically or systemically. If on the other hand, the essential débridement had been well carried out, the patients arrived in good condition, even in those instances in which chemotherapy had been omitted or given in subtherapeutic doses.

The results in these closures were not appreciably altered by either sulfonamides or penicillin locally or systemically when given at the time of closure. The principle of closure of wounds has progressed to the point that it is

perhaps justifiable to postulate that superficial wounds not closed or covered by graft within 3 or 4 weeks of receipt of injury are being improperly treated. The deterioration of muscle, fascia, tendon, blood vessels, and bone when exposed in an open wound progresses at an alarming rate and most of the complications of wounds can be prevented by covering them with epithelium. This procedure is only possible when accurate and complete débridement has been carried out. In many cases in which débridement has been improperly done or omitted entirely it is feasible to carry out this essential part of the treatment some days later at a fixed installation. It has been stated that débridement was accomplished by surgeons of the last war only after considerable experience and error. However surgeons of this war were well versed in this particular phase of the emergency treatment of wounds. This factor is undoubtedly of prime importance in the consideration of the excellent results that were obtained.

Opinions concerning the plaster treatment of compound fractures are likewise rather universally being revised. There is no question but that the plaster method as outlined by Trueta is an excellent method for carrying our emergency treatment of wounds under battle conditions, permitting rapid evacuation of wounded with a minimum of trauma. Unfortunately there has been misinterpretation on the part of many as to the applicability and this method has been employed on a large scale in some centers for the definitive treatment.

There were only 5 or 6 instances of secondary hemorrhage. This infrequent occurrence may be attributed to the lack of infection and deterioration of tissue which is presented by prompt wound epithelialization. There were only 3 deaths which can reasonably be attributed to any operative procedure in 2,915 operations performed upon this group of patients. Death in these cases was due to pulmonary embolism. Of 4,471 patients discharged from the surgical service less than 5 per cent left with a wound requiring any dressing whatsoever. All soft part wounds have been epithelialized, either by closure or grafting, and practically all compound fractures have been covered with skin either by closure or grafting. The notable exceptions have been wounds of the foot with extensive loss of skin and infection of the small bones of the foot, many of which had persistent and resistant sinuses despite best efforts at closure.

SUMMARY AND CONCLUSIONS

1. The 725 secondary wound closures of so-called contaminated wounds resulted in satisfactory healing.

2. The results in secondary closures are not appreciably altered by either sulfonamides or penicillin when applied locally at the time of closure.

3. One of the most important factors which has allowed surgeons to close compound fractures and large soft tissue defects, often times many days after the original wound, is the security afforded by the knowledge that one possesses an agent (systemic penicillin and sulfonamides) which successfully combats hemolytic infection and prevents septicemia.

4. Secondary closure of *granulating* wounds can only be successfully performed when secondary débridement is carried out.

The capacity for regeneration and repair as related to wound healing involves certain fundamental principles. To speak of the wounds of warfare categorically and to consider them apart from the traumatic and surgical wounds of civilian life may lead to certain omissions in the consideration of the general features of wound healing. Present experiences indicate more than ever the importance of a sound knowledge of the basic fundamentals of surgical principles. Careful débridement skillfully carried out is still the one most important single treatment for wounds. Without it, no supplementary form of treatment will succeed. Although conditions may be far from ideal the principles of peace time surgery continue to be perfectly valid in times of war.

MASCULINIZING TUMORS OF THE OVARY

A Clinicopathologic Survey with Discussion of Histogenesis and Report of Three Cases

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INCREASING numbers of masculinizing tumors of the ovary are reported in the literature.

The histological appearance of the arrhenoblastoma group heretofore has occasioned little difficulty in pathologic diagnosis. More confusing are those few cases associated with virilizing symptoms which, because of their microscopic appearance, have been variously termed hypernephroma of the ovary, masculinovoblastoma, ovarian adrenal rest, or adrenal cortical inclusion. Sometimes classified with the "virilizing lipoid cell" tumors of the ovary and often indistinguishable from them are the luteinomas or luteomas.

Two of the following cases illustrate interesting variations of the more typical findings of arrhenoblastoma. Case 3 represents both of the above general histologic types in intimate association and is reported for its contribution to the understanding of the histogenesis of these tumors.

CASE 1. Mrs. C. L. D., Duke Surgical Pathology No. 5636. The patient was 37 years of age, white, a nullipara with a previous history of regular menstrual periods and an oophorocystectomy at 17 years of age. Her present illness was of 18 months' duration, the onset marked by amenorrhea and followed by growth of coarse black hair over her face and chin. In addition to the hoarseness of her voice she noted a tendency to perspire easily, and nervousness accompanied by bitemporal headaches. A slight weight loss and mild lower abdominal pain were experienced during the last few months of her illness.

Patient's height was 63 inches: weight, 163 pounds; blood pressure, 144/100.

The patient's face and chin were covered by a growth of hair about 1 inch in length. There was no temporal recession of the hairline. Some coarse hair was distributed about the breasts, which were of normal size. A moderately tender cystic mass occupied the right lower abdomen extending up to the umbilicus. Appearance of clitoris and vocal cords were not recorded.

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At operation a large cystic mass was found in the region of the right ovary. The left ovary was small and firm. Three small pedunculated fibromyomas were removed from the uterus, together with the entire ovarian tumor.

After operation the headaches disappeared immediately and menstruation began shortly after discharge from the hospital. The hirsutism diminished, and after 10 years the patient remained free of symptoms of recurrence.

Accessory clinical findings: hemoglobin, 90 per cent; leucocyte count, 8,600; differential, normal. Urea, 28 milligrams per 100 cubic centimeters; Wassermann, negative. Glucose tolerance test (50 mgm. of glucose given): fasting, 80 milligrams; first hour, 125 milligrams; second hour, 118 milligrams; third hour, 77 milligrams. Urine: clear; Bence-Jones protein present. Basal metabolic rate, +7.

Pathologic examination. The gross specimen consisted of a mass measuring 16 by 8 by 6 centimeters and weighing 1500 grams. The outer surface was smooth except for several cystic areas on the surface. In the center was a well circumscribed semisolid area, grossly hemorrhagic. Numerous multilocular cysts with thin gray walls occupied the rest of the tumor.

The microscopic sections revealed ovarian cortex with primitive follicles at the periphery of the mass. Many large hemorrhagic cysts lined by macrophages containing hemosiderin were noted. There was an imperceptible transition between ovarian mesenchyme and tumor stroma, which, for the most part, appeared very edematous and myxomatous. In the myxomatous tissue were clumps and columns of large polyhedral cells with dark staining eccentrically placed nuclei and granular or foamy eosinophilic cytoplasm. These cells were especially abundant about the periphery of masses of sarcoma-like tissue consisting of whorls of elongated spindle-shaped cells (Figs. 9, 13, 15 *O*). The latter in some areas were rounded, resembling granulosa cells, and in others ovarian stroma.

The histological picture of the ovarian mass was almost identical with that of 2 cases of arrhenoblastoma with metastases seen in this laboratory (Table I, Cases 38 and 41). One of the latter patients died within 2 years after removal of the primary tumor; the patient just described was free of symptoms of recurrence for at least 10 years after operation.

TABLE I.—ARRHENOBLASTOMA: CLINICAL AND

Author Year	Type*	Age (years) Race	Duration	Weight loss	Pain	Abdominal swelling or palpable mass	Loss of libido	Hirsutism	Voice change	Amenorrhea	Hypertrophy of clitoris	Atrophy of breasts	Hormonal assays
1. Baldwin and Gafford, 1936	II	24 C	9 yr.	O	+	+	O	+	O	+	2.5 cm.	+	Friedman test neg.
2. McLester, 1936	II	32 W	3 yr.	+	O	+	O	+	+	+	3 cm.	+	
3. Behrend and Levine, 1936	I	52 W	4 yr.	O	O	+	O	O	O	Lifetime	O		
4. Maxwell, 1937	Atypical	61 W	10 yr.	+	O	+	O	+	+	Postmenopausal	+	+	Preoper. urinary estrin 40 mouse un.
5. Von Szathmary, 1937	II & III	25 W	1½ yr.	+	O	+		+	+	+	+	+	Preoper. no estrogens; postop. 130 mouse units
6. Haffner, 1937	Atypical	32 W	2 yr.	O	O	O	O	+	+	+	+	+	Preoper. 18 mouse units
7. Fœderl, 1937	III	17 W	2 yr.	O	+	+	+	+	+	+	+	+	
8. Miller, 1937	I	39 W	1 yr.	O	O	+	O	O	O	+	O	O	
9. Dudman, 1938	I‡	18 W	4 yr.	O	+	+		O	O	+	O	O	
10. Norris, 1938	II?	34 W	3 yr.	+	O	O	O	+	O	+	O	O	
11. DaCosta, 1938	II?	66 W	6 yr.	O	O	+	Always	+	O	Postmenopausal	5 cm. menopausal	+	
12. Novak, 1938	I	35 W	11 mo.	O	+	O	O	+	+	+	4.5 cm.	+	
13. Novak, 1938	II	24 W	2 yr.	O	O	O		+	+	+		+	
14. Novak, 1938	II	22 W	1 yr.			+		+	+	+		+	
15. Novak, 1938	II	17 W	2 yr.						+	+	+	+	
16. Novak, 1938	I	40 W	? mo.		+			O	O	Scant menstruation	O	O	
17. Novak, 1938	III	34 W	7 mo.					+		+			
18. Spilling (Case 1), 1938	III	19 W	2 yr.		+	+	O	+	+	+	+	+	
19. Spilling (Case 2), 1938	II	20 W	2½ yr.			+		+	+	+	+	+	
20. Mass. Gen. Hospital, 1939	III	29 W	9 yr.	+	O	O	O	+	O	+	+	+	Androgens 8.5 mgm. 6.3 mgm.
21. Canelo and Lisser, 1939		29 W	2 yr.	Gain at onset	+	+	O	+	O	+	O	+	
22. Dockerty and MacCarty, 1939	II	25 W	2½ yr.	Gain 20 lbs.	+	O	O	+	O	+	+	+	Prolan 66 units
23. Dockerty and MacCarty, 1939	I	31 W	2 yr.	O	O	+	O	+	O	+	O	O	
24. Dockerty and MacCarty, 1939	II	15 W	2 yr.	O	O	O	O	+	+	+	+	+	Prolan and estrin O

MORPHOLOGICAL FEATURES OF 41 CASES

Blood pressure	Blood sugar (mgm. per cent)	Basal metabolic rate	Weight of tumor (grams)	Size of tumor (centimeters)	Marked cystic changes	Atrophy of uninvolved ovary	Recurrence	Improvement	Remarks
120/70		+7	2100	27x11	+	+	0	4 mo.	Bone in one portion of cyst wall. Laparotomy 4 mo. after operation showed normal ovary on opposite side
		+36 to 41	930	17	+	+	0	10 da.	Mucous cyst and rete testis noted in involved ovary
			1030	20	0	0	0		Vaginal atresia, absence of cervix, rudimentary uterus
220/100	97	+39		4x1.5	0	+	0	1–4 mo.	Schiller interpreted tumor as adrenal cortical neoplasm. Cells were polygonal and spindle shaped
							1½ yr.	1–3 mo.	Mixed type at first operation, ascites. Sarcomatous at second operation
				14				+	Large numbers of interstitial cells
				15	+	+	0	24 da.	Cells spindle shaped and some containing small vacuoles are arranged in epithelial strands
				7x7	0	0	0		Adenoma tubulare
				7	+	+	0		Absence of internal genitalia. Testicular tissue in place of ovary
150/80	154–234		4.8	15x11	+/–	0	Died	0	Autopsy: metastases to liver, mediastinum, adrenals. Pigmentation of skin
165/100				7	+	0	0		Tumor also contained granulosa cells
				5.5	0	+	0	12 wks.	Grossly hemorrhagic appearance of tumor. Some areas have definite tubules, resembling rete tubules of ovary; in others spindle-cells, and in others polyhedral cells
				9x8x6	+		0	1 mo.	Sarcoma-like in some areas; in others cells arranged in columns. Also collections of polyhedral cells. Great deal of necrosis
				9	+		0	+	Some portions tubular where compact cells arranged in cords. After 3½ yrs. patient still shaving and voice deep. Menstruation regular
					0		0	1 mo.	Spindle cells, as well as cords, tubules and a few areas of polygonal cells; Leydig cells. All symptoms disappeared after 3 mos. Acne
				10	0		0	+	Looks like seminiferous adenoma
				10x9x6	0		0	1 mo.	Mostly sarcomatous with spindle cells. Also occasional tubules, but imperfect. Few polygonal cells
			1200	20x20	+		+ Died	+	
			345	15	+		0	4 wks.	
90/60	57			5x3	0	0	0	1 mo.	Leydig cells mixed with adenoma tubulare
120/80	83	–6			0		Died	0	Pituitary cyst; brief period of improvement following hypophysectomy, then ascites and abdominal mass. Metastatic interstitial cells. Primary disease simulated Cushing's
98/60		–9		5	0	0	0	1 mo.–2 yr.	No abnormal distribution of fat. Pregnancy 1 yr. later
165/90				20x15	0	0	0	+	Epithelium similar to that forming tubular structure, minimum lipids
118/89		–7		1x6	0	0	0	3 mo.	Acne; lipoid present in large pale interstitial cells

TABLE I.—ARRHENOBLASTOMA: CLINICAL AND

Author Year	Type*	Age (years) Race	Duration	Weight loss	Pain	Abdominal swelling or palpable mass	Loss of libido	Hirsutism	Voice change	Amenorrhea	Hypertrophy of clitoris	Atrophy of breasts	Hormonal assays
25. Dockerty and MacCarty, 1939	?	51 W	2 yr.	0	0	0	0	0	0	Post-menopausal menorrhagia	0	0	
26. Sarkar and Tribedi, 1939	II	18 Hindu	22 mo.	0	0	+	+	+	+	+	+	+	
27. Boltuch, 1940	II & III	28 W	2 yr.	+	+	0	+	+	+	+	4.5	+	Female hormones increased, Male —same
28. Kanter and Klawans, 1940	III	33 W	4 yr.	Gain 58#	+	+	+	+	+	+	3X normal	+	Preop. 51 capon units; postop. 5 capon units
29. Kanter and Ragins, 1941	II	47 W	1 yr.		+	+	0	+	0	+	+	+	
30. Mass. Gen. Hospital, 1941	I	53 W	2 yr.?	0	+	+	0	+	0	Post-menopausal	+	0	17 ketosteroids 3.9 mgm. & 5.5. mgm. in 24 hrs.
31. McIntyre, 1942	II	26 W	2 yr.	0	0	+	0	+	0	+	3	0	
32. Lisser, Palmer and Morton, 1942	II	25 W	1 yr.	0	+	0	0	+	0	+	2	+	Pregnandiol 0 Gonadotropins 0
33. Collins, Beacham and Schattenberg, 1942		42 C	4 mo.	0	+	+		+	+/0	+	7.2		
34. Johnson, 1944	II	24 C	8 yr	0	+	+	0	+	+	+	2.5	+	
35. Pires, 1944		22 W	20 mo.	Gain 20 Kg.	+	+		+	+	+	+	+	
36. Hartz, 1945	II	20 C	15 mo.	+	0	+		+		+	3.5	+	
37. Brentnall, 1945		26 W	9 mo.?	+				+	+		+	Hypertrophy	
38. Davis and Hamblen (in press), 1946	II	37 W	2 yr.	+	+	+	Increase	+	+	+	+	+	Preop. androgens 139 mgm.; Postop. 79–121 mgm.
39. Iverson (Case 1), 1946	II	37 W	1½ yr.	+	+	+	0	+	+	+		0	
40. Iverson (Case 2), 1946	II	31 C	1½ yr.	+	+	+	Postop.	+	+	+		+	Postop. ketosteroids 3.3 mgm.
41. Iverson (Case 3), 1946	II & III	61 W	17 yr.?	0	+	+	Always	+	+	Post-menopausal	2.5	+	

*Types: I—Adenoma tubulare testicular; II—Mixed; III—Sarcomatous.
‡Dysgerminoma.
Additional cases of arrhenoblastoma not included in Table I.
1937: Glaser and Haempel.
1938: Varangot; Hitzanides; Xavier and Junqueira; Pires; Anderson; Kleistman.

Bence-Jones proteinuria has not been previously reported in cases of arrhenoblastoma.

CASE 2. Mrs. C. H., Duke Hospital No. B57754. The patient, aged 32 years, colored, multipara, was first admitted to an outside hospital because of abdominal swelling.

Eighteen months before admission her periods became scanty, and amenorrhea ensued. Although a possibility of pregnancy was considered, her breasts became smaller. She noted a slight huskiness of voice and began to pluck the few coarse hairs which appeared on her chin. These signs were masked by the increased abdominal swelling. At laparotomy 8

MORPHOLOGICAL FEATURES OF 41 CASES—Continued

Blood pressure	Blood sugar (mgm. per cent)	Basal metabolic rate	Weight of tumor (grams)	Size of tumor (centimeters)	Marked cystic changes	Atrophy of uninvolved ovary	Recurrence	Improvement	Remarks
					O	O	O	7 yr.	All 3 cellular elements present. Few interstitial cells
105/65				20			O	1 mo.	Tubular structures as well as sarcoma-like areas
110/85		−10		10x9	+	O	O	+	Few interstitial cells at periphery; otherwise sarcomatous
110/80			4640	28	+	+	O	+	Embryonic rete and cartilage noted
108/80				15x17	+/−	O	O	6 wk.	Ascites; lipoid granules in cells
220/100	90			3x2	O	O	O		Brownish vaginal discharge. Tumor grossly yellow
130/80				20x15	O	+	O	1 mo.	Tumor grossly yellow; loss of libido postoperatively
	88	−16	87	7x6	+		O	1 mo.	Myxomatous. Pregnancy 11 mo. postoperatively
126/88	95			2.5	O	+			Fibromyomata uteri
132/100		+26		13	O	O	O	+	Dermoid cyst on left. Infantile uterus and cervix
					O			28 da.	Acne. Zones of definite epithelial proliferation, as well as sarcomatous zones and clear vacuolated large cells like Leydig cells. postop. 3 pregnancies; 1 miscarriage, 2 normal
			2100		+	O	O	2 mo.	Cyst lined by columnar epithelium of entodermal origin. Some portions of tumor resemble granulosa cell tumor; carcinoid also presented in tumor
	Normal			9x7	O				Acne. Interstitial cells in soft matrix. Pregnancy together with glycosuria and arrhenoblastoma symptoms. Child a "pseudohermaphrodite," had 3 "periods." Mother lactated 4 days postpartum. Hirsutism gone after 3 months
140/90	73		500	12x15	+		+	Initially	Metastases to peritoneal surfaces, ascites, pleural effusion; improvement after first operation. Died 4 years after onset
144/100	80	+7	1500	16x8	+	+	O	1 mo.–10 yr.	Bence-Jones protein present in urine
120/100				7.5x7	O		+ Died	Initially	Metastatic to liver and peritoneal surfaces
140/80	127	−13	400	21x17	+	+	O	2 mo.	Arrhenoblastoma associated with adrenal-like tissue

1939: Luzuy; Aburel, Marza, and Dobrovici; Ekers and Harstad; Soetidjo Hardjosoekatmo.
1940: Rao, Menon, and Narayanamurthi; Wijsenbeek and Plate; Xavier and Junqueira; Althabe, dePaola, and Colillas.
1942: Usandizaga and Oliva.
1943: Menon and Veliath.
1944: Medina and Amorim; Brito and Rivero; Velasco and Zapatero.
TOTAL—20 cases.

months after the onset of symptoms an ovarian tumor was found and removed.

The specimen consisted of a single encapsulated tumor mass which measured 7.5 by 7 by 5 centimeters. The outer surface was firm, somewhat nodular, and contained a thin walled 2 centimeter cyst filled with straw colored fluid. The remainder of the specimen was a solid tumor-like growth. The cut surface appeared homogeneous, somewhat fibrous in character, and had a slight yellowish discoloration. Scattered through the deeper part of the specimen were small areas of cystic degeneration.

Microscopic sections revealed the tumor to be composed of interlacing spindle-shaped cells with

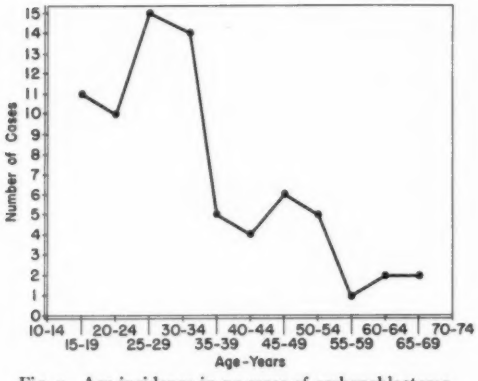

Fig. 1. Age incidence in 75 cases of arrhenoblastoma.

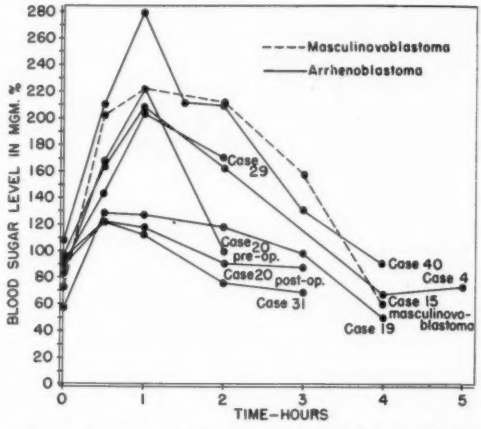

Fig. 2. Glucose tolerance test in 7 cases of masculinizing ovarian tumor.

elongated vesicular nuclei surrounding large plump cells which were typical of the usual "interstitial cells" in arrhenoblastoma.

Transitions from the former primitive type to the latter differentiated cell were prominent. There was abortive tubule formation (Fig. 3).

The patient improved slightly after the operation but noticed no permanent regression of her symptoms. Her weight loss increased to 50 pounds, and she complained of a loss of libido. Five months after operation a marked ascites and left hydrothorax brought her to the out-patient clinic of this hospital. Because of her progressively weakening condition she was admitted and a diagnosis of Meig's syndrome was considered. At this time the original slides were requested and reviewed. Diagnosis of arrhenoblastoma was made.

Accessory clinical findings: Pleural and abdominal fluid: no tumor cells. Hemoglobin, 12 grams; erythrocyte count, 4.13 million; leucocyte count, 9,960 with normal differential. Sedimentation rate, 44 millimeters per hour. Urine, clear. Tuberculin, negative. Total protein, 6.3 grams; albumin 2.7 grams per 100 cubic centimeters; globulin, 3.6 grams per 100 cubic centimeters; 17 ketosteroids averaged 3.1 milligrams per 24 hours for 3 days.

The patient was operated upon 2 weeks after admission to the hospital. Exploration revealed generalized metastases studding the peritoneum and serosal surfaces of the intestines. The thickened omentum was drawn up to the transverse colon. There were metastases to the liver, the surface of which was roughly nodular. Biopsy specimens were taken from the omentum, parietal peritoneum,

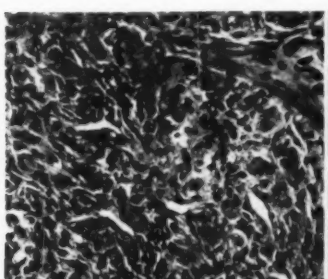

Fig. 3.

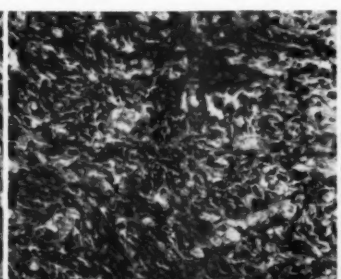

Fig. 4.

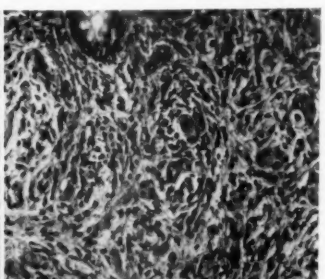

Fig. 5.

Fig. 3. Case 2. Section from primary tumor. Note spindle shaped cells, vascularity, and abortive tubule formation. There are numerous gradations between primitive mesenchymal cells and eosinophilic polyhedral "interstitial cells." ×175.

Fig. 4. Case 2. Metastasis to fallopian tube. Many fat-laden polyhedral cells are intermingled with spindle cells. Note similarity to Figure 14. ×175.

Fig. 5. Case 2. Metastasis to appendix. Note eosinophilic "interstitial cells" in submucosa of appendix, more closely resembling those of primary tumor than of tubal metastasis. ×175.

Fig. 6. Case 3. Lateral view demonstrating distribution of fat. Note hairy arms and legs.

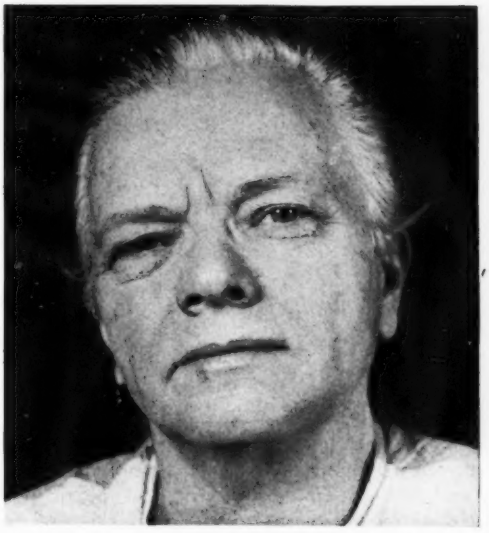

Fig. 7. Case 3. Patient before operation (after shaving), showing temporal recession of hair line, loss of hair on scalp, masculine features.

appendix, and tube. The patient died 2 weeks after operation, 18 months after the initial symptoms. No autopsy was obtained.

All of the sections showed metastatic tumor, the microscopic appearance of which varied greatly. The surface implants were characterized by a friable mass of fibrin, necrotic débris, and large cells resembling "interstitial cells." Infiltrating or metastatic lesions were accompanied by more connective tissue and primitive stroma in the meshes of which were numerous fat laden foam cells (Fig. 4). The latter, where found in the appendix, contained less fat (Fig. 5) and more closely resembled the original eosinophilic interstitial cells.

Because of the early metastasis of this tumor and the rapid growth of primitive cells, functional signs were slight. Masculinizing symptoms were elicited only in retrospect. The ascites and hydrothorax resulting from the widespread metastases led to a clinical diagnosis of Meig's syndrome before the second hospital admission. The original tumor presented a relatively benign appearance at a time when there was already evidence (ascites) of early metastasis. The varied and baffling histological picture of the metastatic implants and their dissimilarity to the primary mass re-

Fig. 8. Case 3. View of enlarged clitoris, which measured approximately 2.5 centimeters.

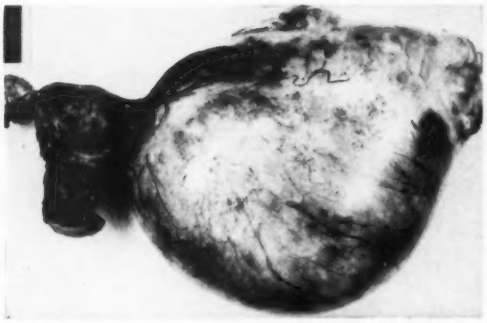

Fig. 9. Case 3. Operative specimen including uterus and adnexa. Note small uterus and atrophic right ovary. The left tube roughly marks the boundary of the large thin walled cyst below and the nodular multicystic tumor mass above.

Fig. 10. Case 3. Cross section of left ovarian tumor viewed from behind. Note thickening of medial portion of large cyst wall. Small nodular masses in cyst wall showed a sarcomatous pattern with absence of interstitial cells. Other small nodules scattered throughout the gelatinous tumor mass above the large cyst contained varying proportions of spindle cells and interstitial cells. Tumor nodules *A* and *B* represent the gross picture of arrhenoblastoma and adrenal-like tissue, respectively.

moved 10 months previously emphasize the need for careful clinical and pathologic investigation of every case of primary ovarian neoplasm.

Case 3. Miss J. S., Duke Hospital No. B54444. The patient, aged 61 years, a single white female, nullipara, was admitted to the hospital complaining of a pelvic tumor of 2 years' duration. Her mother and maternal grandmother had facial hirsutism, but there was no family history of masculinizing tumors. Her father and one brother had diabetes mellitus. The patient stated that her flat hips, large abdomen, sway-back, and unusual physical strength were "inherited" from her father. The essential features of her development and illness are summarized as follows: Age 10: Reached maximum height, maturing at same rate as sister. Axillary and pubic hair appeared. Age 13: Menarche; periods regular every 28 days, lasting 4 to 5 days; normal flow. Age 15: Weight 126 pounds, maintained for 10 years. Age 25: Increase in hair on chest, upper lip, side of face, controlled by plucking the more unsightly areas. Age 26: Began to gain weight, slowly attaining maximum weight of 155 pounds. Age 35: Heavy hair appeared on arms and legs. This persisted, but there was no change in axillary or pubic hair. Age 44: Forced to begin shaving of hair on cheeks, upper and lower lips, and neck. Age 55: Spontaneous menopause, characterized by mild nervousness and "hot flushes." Age 58: (2½ years before admission). Pain in knees and back upon exercise. Abdominal swelling. Diagnosis of local physician: arthritis; fibroid tumor "size of grapefruit." Age 59: (1½ years before admission). Voice became harsh and continued to assume a lower pitch and coarser quality. Age 61: (Six months before admission). Slight vaginal bleeding every day for 5 months.

The breasts were reported as having always been small. The patient admitted no change in emotional make-up or sexual desire with her illness. She received no hormonal therapy.

Physical examination revealed temperature, 37 degrees; pulse, 72; respirations, 20; blood pressure, 140/80.

The patient was a co-operative, intelligent woman whose manner was conventional and feminine, and whose voice was slightly hoarse but well within a feminine range. The hair was gray or white and quite sparse, especially at the temporal region. There was evidence of recently shaved beard over the face and neck (Figs. 6, 7). Heavy black hair was distributed over the shoulders and became quite long and coarse over both forearms and the entire surface of the muscular legs. The pubic hair had a masculine distribution, pointing upward toward the umbilicus. The skin was coarse in texture, and the chest suggested a buffalo distribution of fat. The breasts were extremely small, flat, with pale pink nipples and areolae surrounded by a ring of fine black hair. There was no hair between the breasts.

Both vocal cords were slightly reddened posteriorly and moved on phonation. The thyroid was not palpable. The abdomen was slightly protuberant. A firm, mobile, painless mass rose from the pelvis to the level of the umbilicus.

There was moderate hypertrophy of both labia majora and minora. The clitoris was hypertrophied, attaining a length of 2.0 to 2.5 centimeters and a diameter of 1 centimeter (Fig. 8). There was a nulliparous introitus of excellent support. The cervix was small, conical, and firm. The uterus was not palpable and appeared to be separate from the large mass, which extended into both adnexal regions.

Accessory clinical findings: Roentgenograms of the skull showed no change in the sella turcica. Retrograde pyelograms revealed a slight dilatation of the

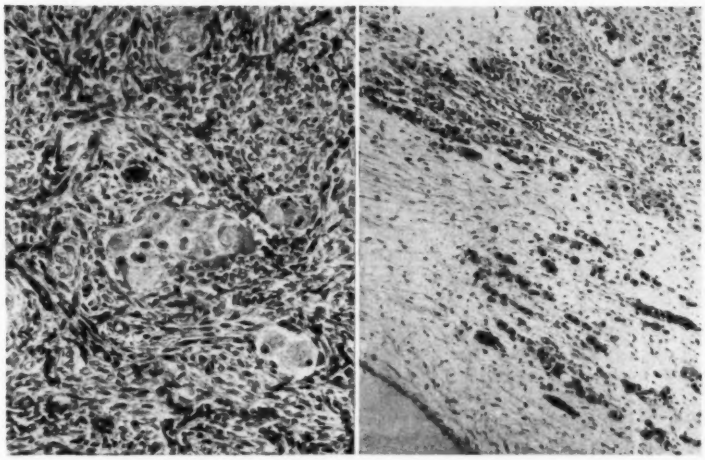

Fig. 11, left. Case 3. Microscopic section of tumor nodule *A* (Fig. 10). Note large polyhedral "interstitial cells" within the sarcomatous tissue. This section resembles primary tumor seen in Case 1. ×170.

Fig. 12. Case 3. Microscopic appearance of edge of a small cyst. Note lining up of "interstitial cells" in loose connective tissue. Tumor nodule *B* was composed of a large area such as this. At upper right is seen the periphery of a small mass similar to tumor *A* (Fig. 11). ×85.

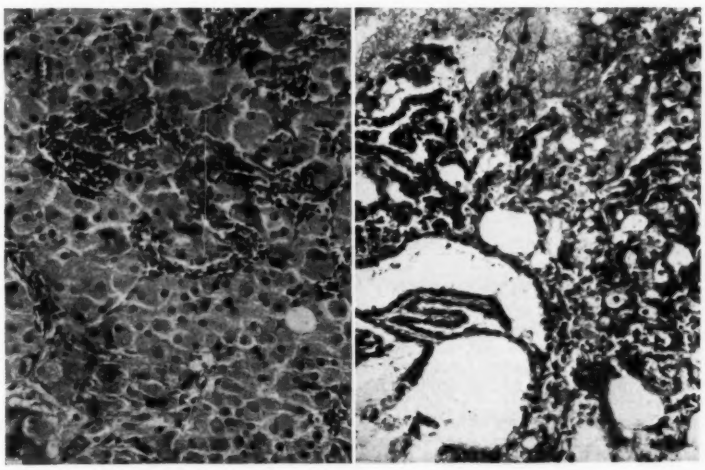

Fig. 13, left. Case 3. Microscopic appearance of a small nodule (*C* in Fig. 10). Compare with interstitial cells in Figure 11. Note foamy appearance of cells, comparatively slight stroma, marked vascularity and great variation in cell size. ×170.

Fig. 14. Case 3. Microscopic section of peritoneal implant. This was the only metastasis and contained fat-laden polyhedral cells resembling those in metastatic lesion in Case 2 (Fig. 4). Note similarity of these cells to those in masculinovoblastoma (Fig. 15*P*). Interesting tubular structures characteristic of intermediate types of arrhenoblastoma were not seen in primary tumor.

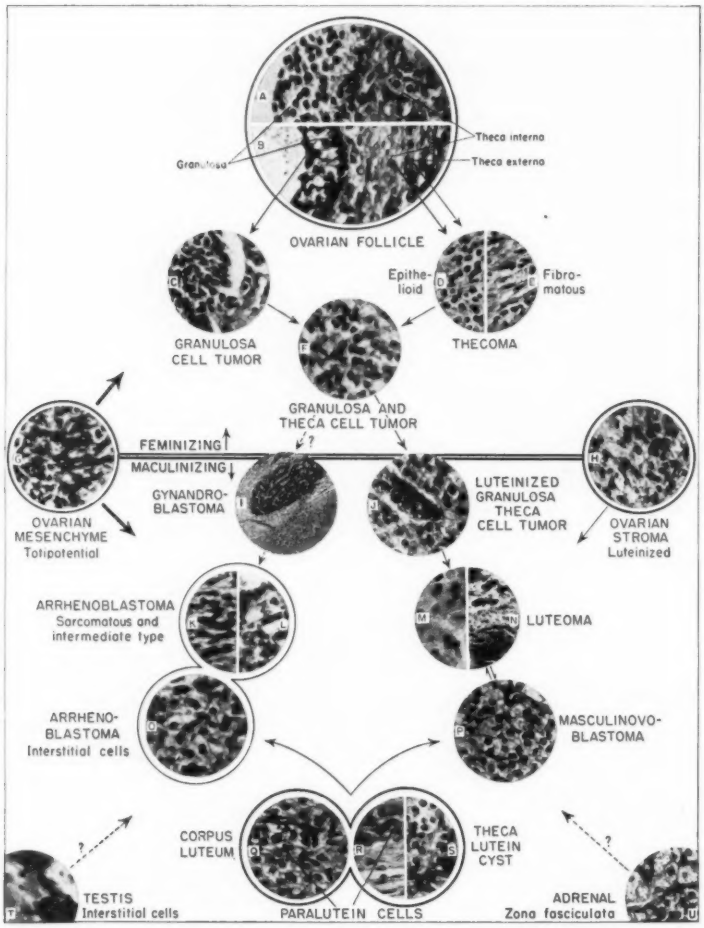

Fig. 15. Morphological interrelationship of functional ovarian tumors and normal ovarian structures.

The chart shows the ovarian tumors divided into the feminizing and masculinizing groups by a line connecting two pictures of ovarian stroma: *G*, the relatively undifferentiated primitive mesenchyme which is totipotential; and *H*, the luteinized ovarian stroma.

At the top center are seen two pictures of an ovarian follicle, *A* and *B*, showing the three layers of the follicle and the corresponding tumors, so named because of their morphological resemblance to the granulosa and theca cells. Two examples of thecoma are included to show the more cellular type resembling the theca interna, *D*, and that which resembles fibroma, *E*, morphologically similar to the cells in the theca externa. Combinations representing both types of feminizing tumors are frequently seen, *F*.

There are two main groups of frankly masculinizing tumors, the arrhenoblastoma, *O*, and the masculinovoblastoma, *P* (adrenal cortical rest, virilizing lipoid cell tumors, etc.). *K* shows the sarcomatous type of arrhenoblastoma in a large metastatic growth, the more frequent histological appearance of metastatic arrhenoblastoma (Figs. 4, 5, 14). *L* represents the primary tumor in the same case (Table I, Case 38), demonstrating the tubular form which suggests somewhat the follicular type of granulosa cell tumor.

O shows a cluster of interstitial cells at the periphery of a sarcomatous arrhenoblastoma nodule (Case 1) resembling the larger masses of such cells seen in the adrenal-like tissue of Case 3 (Fig. 13). Note the similarity to luteinized ovarian stroma, *H*, paralutein and theca lutein cells, *Q*, *R*, *S*, and masculinovoblastoma, *P* (Table II, Case 24).

These morphological similarities would suggest that arrhenoblastomas may represent neoplastic growths from totipotential ovarian mesenchyma, *G*, *H*, rather than from embryonic testicular structures. (See text for further discussion.) They further suggest the fact that masculinovoblastoma may actually represent a neoplasm of "interstitial

(*Legend continued on opposite page.*)

right pelvis and ureter. Vaginal smear consisted almost entirely of débris and degenerated cells; very rarely an atypical epithelial cell was seen. The smear indicated extreme hypoestrogenism (Mack, Grade 1). There was some spilling of sugar in the urine during the glucose tolerance test, and blood level indicated a decreased tolerance to glucose, suggesting a diabetic tendency: fasting specimen, 108 milligrams; ½ hour, 210 milligrams; 1 hour, 280 milligrams; 1½ hours, 212 milligrams; 3 hours, 131 milligrams; 4 hours, 90 milligrams. Blood sugar, 103 milligrams; total proteins, 7 grams; chlorides, 600 milligrams; cholesterol, 150 milligrams; calcium, 8.4 milligrams. Basal metabolic rate, −13. Serological tests for syphilis, negative. Urinary assays of ketosteroids: preoperative, 10.9 milligrams per 24 hours; postoperative, 8.85 milligrams per 24 hours. Preoperative gonadotropins: 12 rat uterine units, 6 rat ovarian units, 4 rat macroscopic corpus luteum units. Postoperative gonadotropins: 18 rat uterine units, 10 rat ovarian units, 4 rat macroscopic corpus luteum units.

The following diagnoses were made: arrhenoblastoma; adrenal cortical neoplasm or hyperplasia; adrenal rest tumor of the ovary.

On the 18th hospital day, operation was performed. A large cystic tumor about 25 centimeters in diameter was found replacing the left ovary. Following an uneventful recovery the patient was discharged on the 29th hospital day. Four months later, she wrote, "Everyone marvels at my quick recovery. The hair on my face and arms is not so thick, about half as much as before the operation. A few new hairs are growing on top of my head where the baldness was taking place. My voice is remarkably better. I can sing a little, which I had been unable to do in almost a year and one half."

The gross specimen consisted of a uterus and bilateral adnexa (Fig. 9).

The uterus was 8 by 6 by 5 centimeters and contained four small intramural fibromyomas. A soft grayish polyp projected into the endometrial cavity from the superior fundic wall. The right ovary was fibrous, indurated, and obviously atrophic. The right tube showed no gross lesions. The left tube was stretched to a length of 10 centimeters as it coursed up to the superior pole of a large 21 centimeter cyst, containing clear yellow fluid.

The lateral and inferior cyst walls were paper-thin, and numerous tortuous veins were prominent over the surface. Bordering the thicker superior cyst wall was a rough boggy mass which was divided by fibrous septa into several polycystic gelatinous masses. The largest of these was located in the superior lateral curvature of the cyst wall and was composed grossly of grayish-green myxomatous tissue, in the center of which were two separate and distinct nodules. The first (tumor *A* in Fig. 10) was a firm white tumor, 2 by 1.5 centimeters; the second (tumor *B* in Fig. 10) was a soft, bright orange, irregular mass, 3 by 2 centimeters. Scattered throughout the myxomatous stroma were numerous tiny yellow flecks of varying size and shape. In some areas these assumed a well circumscribed soft white nodular form with no gross encapsulation. The various septa appeared to converge posteriorly as a band of white fibrous tissue, 0.5 to 1.5 centimeters thick, gradually thinning out toward the medial surface of the cyst.

Microscopic sections revealed a chronic vaginitis and cervicitis. The endometrial polyps were characterized by an atrophic stroma and cystic, nonfunctioning glands. The small intramural and surface nodules proved to be fibromyomas surrounded by edematous myometrium.

No ovarian tissue could be demonstrated on the left. Many sections of the cyst wall showed dense collagenous fibrous tissue interspersed with myxomatous tissue. No evidence of teratomatous growth was found. The yellowish nodule in the midst of the wall where the Fallopian tube ended showed a sarcomatous pattern with an imperceptible transition to myxomatous or fibrous tissue at its border. Parts of the more compact regions of the cyst wall were hyalinized, and at the edge of the larger gelatinous mass there was an abrupt transition between the fibrous capsule and the myxomatous stroma.

Tumor *A* was composed of spindle-shaped cells with elongated vesicular nuclei which were marked by a clear nuclear membrane and two or three nucleoli. The larger nuclei contained a coarser chromatin network than the smaller, more compact nuclei. Gradations toward the "interstitial cell" described below were frequent. Bipolar strands of cytoplasm containing minute fat droplets were so interlaced that cell borders could not be distinguished. The tumor was not encapsulated, but ap-

cells" shown to be morphologically similar to theca lutein or paralutein cells (Table III).

Gynandroblastomas, *I*, and luteinized granulosa or theca cell tumors or both, *J*, are both histologically and clinically borderline. Luteomas, *M*, *N*, are completely luteinized granulosa or theca cell tumors or both and may be masculinizing or feminizing. The tumor shown at *J* was masculinizing; others histologically similar may be feminizing.

Some workers include masculinizing luteomas within category of virilizing lipoid cell tumors or masculinovoblastoma. This relationship is shown by double arrow connecting *M*-*N* and *P*.

Note morphological similarity of luteoma *M*, *N*, to paralutein cells, *R*, rather than to lutein cells at right of *Q* (more accurately termed "paraluteinoma"?). There is a resemblance between androgen and progesterone-producing paralutein cells, *Q*, and theca lutein cells, *S*, and those of masculinovoblastoma, *P*.

Former theories relative to the histogenesis of the two types of masculinizing tumors are represented by photographs of a normal testis showing interstitial cells of Leydig, *T* and of a normal adrenal, zona fasciculata, *U*, showing cells similar to those in the masculinovoblastoma. The morphological gradations between tumors known to arise from ovarian structures (totipotential ovarian mesenchyme) and the masculinizing tumors strengthen the histogenetic relationship of the theca lutein or paralutein cell to arrhenoblastoma and masculinovoblastoma.

TABLE II.—ADRENAL TUMORS OF OVARY: CLINICAL

Author Year	Age (years)	Race	Duration (years)	Weight loss	Pain	Abdominal swelling or Palpable mass	Loss of libido	Hirsutism	Voice change	Amenorrhea	Hypertrophy of clitoris	Atrophy of breasts	Hormonal assays
1. Bovin, 1908	28	W	7	O	+	+		+		+		O	
2. Bingel, 1924	47	W	17(?)	Gain		+	Incr. toward9	+	+?	+			
3. Sellheim, 1925	49	W	6	Gain		+	+	+	+	+	4 cm.	O	
4. Cosacesco, et al, 1931	34	W	8	O			+	+	+	+	3-4 cm.	+	
5. Saphir and Parker, 1936	15	W	1	Gain 30#	O	O		+	+	+	O	+	Gonadotropin (urinary).66 mouse un. Estrogens increased
6. Stadiem,* 1937	39	W	2-3	+	O	+	O	O	O	Irregular	O	O	Friedman test: neg.
7. Novak, J. and Wallis, 1937	30	W	2	O	O	O	O	+	+	+	+	+	Folliculin: O Prolan: O Androgensincreased
8. Maxwell, 1937	61	W	10	+	O	+	O	+	+	Post-menopaus.	+	+	Preop. estrin (urinary) 40 mouse units
9. Novak, E. (Case 1), 1938	24	W	4					+	+	+	+	O	
Novak, E. (Case 2), 1938	37	W	3					+	+	+	+	O	Estrin: 4 rat units Androgens: 2-12 mm. comb. growth
10. Schattenberg and Miller (Novak, Case 3), 1938	27	W						+	+	+	+	+	
11. Reis and Saphir* (Case 1), 1938	STILLBORN: NODULAR TUMOR IN CORTEX COMPOSED OF												
12. Reis and Saphir (Case 2), 1938	32	W	4	O	O	+			+	Menor-rhagia			
13. Reis and Saphir (Case 3), 1938		W	2	O	O	+			+	+	O		
14. Van Kirk and* Edwards, 1939	42	W	1	20#	+	+	O	O	O	O	O	O	
15. Rottino and McGrath (Case 1), 1939	23	W	3	16#	O	+	O	+	+	+	+	O	Estrogens: 3.3 units Androgens: 17.3-15.7 int. u.
16. Rottino and McGrath (Case 2), 1939	30	W	5	+	O	+	O	+	+		O	O	
17. Bauer, 1939	32	W	3	Gain				+	O	+	+		
18. Blackmun, 1942	23	W	3½	Gain	O	O		+	+	+followed by menor-rhagia	1.5 cm.	+	
19. Kannerstein* Brown and Rosen, 1943	52	W		O	+	+		O	O	Post-meno-pausal	O	O	
20. Kepler, 1944	16	W	2	Gain		+		+	+	+	3X nor-mal	O	17 ketosteroids 54.6 mg. Estrin 19, prolan <10 rat units per 24 hours
21. Greene and Lapp, 1944	29	C	4	O	LLQ	+	O	+	+	+	4-5X normal	O	

AND MORPHOLOGICAL FEATURES OF 24 CASES

Blood pressure	Blood sugar (mgm. per cent)	Basal metabolic rate	Weight of tumor (grams)	Size of tumor (centimeters)	Marked cystic changes	Atrophy of uninvolved ovary	Recurrence	Improvement	Remarks
				8x8.5x6	+	+	0	2½ mo.	Tumor made up of fat-containing large polyhedral cells. Some other cells did not contain fat but had a granular cytoplasm.
				9x9x4		+	0	+	Polydipsia during last 4 years preoper.; RBC 8.9 million; Hgb. 180 per cent. Tumor cells granular eosinophilic cytoplasm. No fat; large nuclei; lutein cell.
				22?		+	0	3 wk.	Polygonal cells, no fat or glycogen. Large nuclei and nucleolus.
				5	+	0	0	1 mo.	Large uniform cells, fat filled.
130/70	Nor-				+	0	0	4 da.	Some cysts lined by granulosa cells, nests of polygonal vacuolated cells. Hirsutism unchanged after 10 months.
120/80	100	+40		14x12	0		Death after 6 mo.	0	Metastatic hypernephroma.
				3x3.5	0		0	4 wk.	Polycythemia, hyperglycemia improved postop. Tumor resembled lutein and theca lutein tissue, diagnosed as adrenal inclusion by Schiller.
220/100	97	+39		4x1.5	0	+	0	1–4 mo.	Schiller interpreted tumor as adrenal cortical neoplasm. Cells were polygonal and spindle shaped.
				3x2.5					Same case as Rottino and McGrath, Case 2.
130/90	Nor-	−7	25	6	0	0	0	+	Polygonal cells in alveolar arrangement; fat-containing.
				2				2 mo.	

"ADRENAL CORTICAL CELLS"

				5.6x7	+	0	0	Pregnancy	Hyperthyroidism followed by hypothyroidism and menorrhagia, preop.; "adrenal cortical cells" at periphery of corpus luteum in wall of cyst.
			40	5.5x3.5	0	0	0	6 mo.	Tumor resembles corpus luteum.
140/90			2700	23.5x20	+	0	0		1.78 per cent glycogen; fat stains showed little fat; glycogen stains revealed cells packed with large and small droplets.
90/60	72		22	3x2.5	0	+	0	2 mo.	Cells 10–16 microns, polyhedral, nuclei small, eccentric.
130/70				Bilat. —5 cm.	0		3 yr.	1 mo.	Lutein-like; ascites at first operation. Cells 8–16 microns, vascular.
				14x13x5					Operative death. Trabeculation. Cells contain lipoid and have eosinophile granules.
	91			6.5	+	+	0	4 mo.	Ponceau fuchsin stains positive. Cells filled with fat.
					+	+	Died		Autopsy. Hypernephroma of right kidney removed, 11 yrs. previously. Diagnosis metastatic ovarian hypernephroma.
160/110	68		650	15x14x9			0	1 mo.	17 Gm. Hgb. postop. Ketosteroids 2.6 mgm. in 24. Bright yellow tumor. Cells contain lipoid, are polygonal with central nucleus and nucleoli; good number mitoses.
120/70	88			7.5x5	0	0	0	6 mo.	Grossly yellow. Sheets of polygonal fat-containing cells in delicate fibrous strom.

TABLE II.—ADRENAL TUMORS OF OVARY: CLINICAL

Author Year	Age (years)	Race	Duration (years)	Weight loss	Pain	Abdominal swelling or Palpable mass	Loss of libido	Hirsutism	Voice change	Amenorrhea	Hypertrophy of clitoris	Atrophy of breasts	Hormonal assays
22. Burket and Abell, 1944	36	W?	16?	+	+?	+		+	+	16 yr.	0		
23. Brabson, et al., 1945	36	C	1	0	0	0	0	+	0	+	0	+	
24. Hamblen and Davis (in press), 1946	18	W	3	0	0	0		+	+	+	+	+	Pre-op. androgens 147 int. units

*Nonvirilizing; excluded from statistical summary.

Additional cases classified as "hypernephroma" not included in Table II:

1937: Turco (case of "extremely malignant hypernephroma.")

peared to end abruptly at its periphery, where it was replaced by loose myxomatous tissue. Here the vascularity was greatly increased, and clumps of large, polyhedral, eosinophilic cells with small round dark eccentric nuclei were seen. Occasional clumps of these cells were included within the sarcomatous mass (Fig. 11).

Tumor *B* was merely a large concentration of the "interstitial cells." Their nuclei were sometimes slightly oval and irregular but were more often round. The nuclear membrane was clear and the chromatin material coarsely granular. The nucleolus was prominent and usually eccentric. In some areas, the nucleus was more compact and finely granular with a hazy nucleolus. Large giant cells with irregular hyperchromatic nuclei were frequent and mitoses were noted in all sections.

The yellow appearance in the mass was due to the accumulation of the "interstitial cells" in concentrations great enough for their lipoid content to influence the gross picture. Figure 12 indicates the approximate concentration of these cells in tumor *B* and shows their arrangement in the myxomatous tissue at the periphery of a sarcomatous nodule. They were seen singly or in groups throughout the entire large tumor mass wherever the loose connective tissue was found. Some of the smaller nodules noted grossly contained polyhedral cells so closely packed in cords and columns that the tumor resembled a luteinoma (Fig. 11). Others of the small nodules showed an arrangement of cells more typical of arrhenoblastoma and very similar to tumor *A*.

One peritoneal implant was noted in a mass of tissue removed separately at operation. This showed three main types of tissue: actual tubule formation approaching the more differentiated type of arrhenoblastoma; a small area of spindle-shaped cells; and clumps of foamy cells whose cytoplasm was swollen with fat (Fig. 14).

The clinical diagnosis of adrenal cortical neoplasm was justified in this case of an illness with a relatively insidious onset and long duration in a postmenopausal diabetic. However, most of the specimen was typical of arrhenoblastoma, except for the yellowish nodule which resembled adrenal tissue grossly. The identity of the latter with the "interstitial cells" of the arrhenoblastoma was shown by cytological studies. The influence of this variation on the clinical picture is not known. Its significance will be discussed later.

REVIEW OF LITERATURE

A. *Arrhenoblastoma.* The first 25 cases of arrhenoblastoma were summarized in 1932 by Buettner. In 1933 Taylor, Wolferman and Krock claimed the first United States case, which was reviewed 8 years later by the latter two authors (108, 68).

By 1936 the total number of cases was 33. These were comprehensively surveyed by Baldwin and Gafford, who grouped them according to Meyer's classification (81):

I. The adenoma tubulare (testiculare) of Pick. "The most differentiated type," usually unassociated with masculinizing symptoms.

II. A middle group with typical and atypical tubular elements and with solid elements.

III. Atypical tumors, solid or predominantly solid, with atypical tubular elements.

Their major findings are calculated below:

1. Average age: 20.3 years; range: 16 to 33 years.

2. Number of cases: Type I: Nine (Three showed virilizing symptoms. These contained mixtures of cells represented in the other two types and were not pure examples of "adenoma testiculare"). Type II. Ten (All showed

AND MORPHOLOGICAL FEATURES OF 24 CASES—Continued

Blood pressure	Blood sugar (mgm. per cent)	Basal metabolic rate	Weight of tumor (grams)	Size of tumor (centimeters)	Marked cystic changes	Atrophy of uninvolved ovary	Recurrence	Improvement	Remarks
124/78				16x13	O	O	Died 2 wk. post-oper.	Initially	Bluish discoloration of face and neck; hemoglobin normal; cords of smaller, compact cells mixed with polygonal lipoid cells.
				7.5x4.5	O		O	4 mo.	Lipoid-containing polyhedral cells.
128/80		+19	200	7x6	O	O	O	+	No Na-pregnandiol gluconide. No progesterone activity of tumor.

1939: Kleine (primary hypernephroid blastoma, 2 cases). Kreutzmann (atypical malignant hypernephroma).

1943: Neumann (hypernephroma with virilism).

virilizing symptoms). Type III: Fourteen (All showed virilizing symptoms).

3. Frequency of important symptoms: Change in voice or vocal cords, 21; hirsutism, 17; clitoral hypertrophy, 14; amenorrhea, 12; atrophy of breasts, 9.

4. Recurrence of tumor: 5.

5. Return of feminism: 25 (mentioned in 29 cases). A total of 8 pregnancies, 5 in 1 patient, were recorded. Earliest improvement noted was resumption of period within 3 weeks.

Fifty-eight cases have been reported since 1936, to which we have added 3 cases, making a total of 94 cases of arrhenoblastoma. Those reported since Baldwin and Gafford's review are recorded in Table I.

B. Adrenal rest tumor, Luteinoma, etc. The second group of masculinizing tumors is called merely "virilizing lipoid cell tumors" by Barzilai. This name was chosen to avoid confusion of terminology in a group in which rigid diagnostic classifications are made by some workers and in which the same diagnostic terms are used interchangeably by others. In this group Barzilai includes "luteinomas" as well as "adrenal rests" and "interstitionomas."

In 1908 Bovin recorded the first case of "hypernephroma" or "adrenal rest tumor" of the ovary. A critical survey of the status of the lipoid cell tumors, luteomas, and hypernephromas was made by Glynn in 1921, who favored a lutein origin of the primary lipoid cell ovarian neoplasm.

More confusion was created by the indiscriminate use of the term "hypernephroma" which may include metastatic nonvirilizing tumors in the ovary. For example, Stadiem's review in 1937 of "Nineteen cases of hypernephroma of the ovary" included no cases which can now be classified as primary virilizing lipoid cell tumors of the ovary.

In 1939 Rottino and McGrath limited the entire number of virilizing lipoid cell tumors to 7 cases. These and the subsequent reports totaling 14 cases were incorporated into a review by Kepler, et al, in 1944. Seven additional cases of lipoid cell tumor associated with masculinizing symptoms can be included at the present time, bringing the total to 21 cases. These are summarized, with the exception of Neumann's report, in Table II. Four other cases, classified as "adrenal rest" or hypernephroma in recent years, but not associated with virilism, are included in the chart for the purpose of comparison.

Attention must be called to the fact that the above 20 cases include: Sellheim's case containing no fat (Case 30 in Baldwin and Gafford's chart of arrhenoblastoma?); Cosacesco's case which is also included in the series of luteomas by Traut, Kuder, and Cadden (112); Saphir and Parker's case of "adrenal cortical inclusion" in which a definite neoplasm was not found; Maxwell's case, diagnosed as adrenal rest by Schiller, but described as arrhenoblastoma by the author; Reis and Saphir's 2 cases of partial masculinization with lipoid cell tumor. Exclusion of these cases would limit the entire series to 15 cases of complete masculinization with a lipoid cell tumor of ovary and classified as adrenal in origin.

Additional cases of masculinization have been associated with tumors which the authors have separated from the above group and have designated strictly as luteinomas or luteomas. Some of this confusion has persisted because some workers justifiably object to the term "adrenal rest," believing that there is no final basis for such a histogenetic classification. The proponents of the adrenal rest theory, in turn, object to the word "luteinoma." Therefore Rottino and McGrath propose the noncommittal term "masculinovoblastoma;" and Barzilai, wary of new terminology, uses the more descriptive phrase, "virilizing lipoid cell tumor."

The following list of "luteomas" is modified from the series of Traut, Kuder, and Cadden, who separate the 2 groups histologically:

1908	Gardner and McCleary	(Amenorrhea for 8 years)
1913	Massabuau	(No virilizing symptoms)
1918	Gordon	(These cases were originally diagnosed "hypernephroma," later reviewed by Turnbull and reclassified as luteoma. No virilizing symptoms.)
1920	Gordon	
1927	Wolfe	(No virilizing symptoms)
1931	Cosacesco, *et al.*	(See Table 2. Classified as adrenal rest tumor by Rottino and McGrath, Kepler, et al.—Virilizing.)
1937	Torres	(No virilizing symptoms)
1938	Viana	(No virilizing symptoms)
1938	Giampalmo	(No virilizing symptoms)
1942	Mayer	(Virilizing)
1944	Giordano and Haymond	(Virilizing)

The histological similarity of the adrenal rest tumors, luteomas, and luteinized granulosa or theca cell tumors (14, 28, 109, 121) necessitate careful evaluation of the clinical signs for accurate classification. Geist and Spielman (41) suggest that when the tumor is accompanied by signs of masculinization it be considered an adrenal rest tumor; and when it is accompanied by evidence of feminizing influence it be termed a luteinized granulosa or theca cell tumor. Such an evaluation of the more recent cases of luteoma may lead to their reclassification as adrenal rest tumor, as in the case of Cosacesco and coworkers.

CLINICAL DATA

Consideration of the clinical features of these tumors is of the utmost importance in understanding their anatomic relationship. In comparing "virilizing lipoid cell tumors" with arrhenoblastomas it must be remembered that the significance of the data will change as more cases are added to both groups and as diagnostic criteria become standardized.

Age. Figure 1 shows the age distribution of 75 cases of arrhenoblastoma, which corresponds roughly to that of "virilizing lipoid cell tumors."[1] Arrhenoblastoma: average age, 31.86 years; range 15 to 66 years. Masculinovoblastoma: average age, 31.7 years; range 15 to 61 years. These findings do not correspond with the statements of some observers that masculinovoblastomas occur in later life.

Race. Cases of arrhenoblastoma have been reported in Hindu, Spanish, and Latin American women. Five cases of arrhenoblastoma and 2 cases of masculinovoblastoma have appeared in the colored race. There is no record of cases occurring in the Orient.

Duration. The preoperative course of arrhenoblastoma averages 4 years. The majority of cases are of 1.5 to 2.5 years' duration, and the entire series range from 1 to 17 years of symptoms previous to operation. Cases diagnosed as masculinovoblastoma average 4.3 years in duration, ranging 1 to 17 years; and the majority have a duration of 3 years or less.

Weight. Fluctuation of weight occurred in 18 of 33 cases of arrhenoblastoma. Of these, 11 showed weight loss and 5 became more obese, gaining 20 to 58 pounds. Masculinovoblastoma: 8, no change; 6, gain, up to 30 pounds; 5, loss of weight. A tendency toward obesity at the onset of the disease is noted in some instances. Loss of weight occurred in 6 of the 7 fatal cases.

Pain, abdominal swelling, palpable mass. One third of the total number of patients with masculinizing tumors complained of pain. Twice that number exhibited objective evidence of the presence of tumor such as palpable mass or abdominal swelling. The symptoms of pain and abdominal swelling or mass are correlated with the size of the tumor, except for metastatic cases in which ascites may be present.

There is little significant difference between the number of virilizing tumors located on right or left side.

[1] The term "masculinovoblastoma" (Rottino and McGrath) will henceforth be substituted for the phrase "virilizing lipoid cell tumor," "adrenal cortical inclusion," and "hypernephroma."

Loss of libido. A loss of libido occurred in approximately 20 per cent of the patients with arrhenoblastoma where this symptom was mentioned. In one patient libido was increased with the presence of tumor. In others the patient experienced a loss of libido only after the tumor was removed.

Available data showed no correlation between libido and basal metabolic rate.

Sterility. Some women complaining of previous sterility become pregnant subsequent to removal of the tumor. Pregnancy has occurred in 10 to 15 per cent of the cases of childbearing age following operation. In 2 cases (17, 125) pregnancy and growth of the tumor occurred simultaneously. One infant was a pseudohermaphrodite, had an enlarged clitoris, and had 4 "periods" beginning immediately after birth at 28 day intervals.

Hormonal studies. Accurate evaluation of hormonal assays is impossible because of the great variation in standards and methods, and because of the absence of control assays. In general, there is an increase in androgens and decrease in estrogens and gonadotropins. In absence of recurrence, the normal levels are gradually resumed postoperatively.

Virilizing and defeminizing symptoms. The patient may give a past history of long-standing amenorrhea, of moderate excess hirsutism, of masculine habitus, or of unusual strength. Some complain of lack of libido during married life or of sterility for many years.

Usually, however, the onset is more definite, progressing steadily for 1 to 4 years until the tumor is suspected. The degree of masculinization is not correlated with size or histological appearance of the tumor, except in patients with those tumors classified as adenoma tubulare.

1. Amenorrhea: Scant menstruation was present in one patient with arrhenoblastoma (Type I). In all other cases complete amenorrhea occurred, including 5 which were postmenopausal. Amenorrhea is usually the first symptom to appear; and after the tumor is removed the periods may return within 1 month.

Menorrhagia sometimes precedes the amenorrhea. In some cases it is associated with polyps and fibromyomata uteri; in others the significance is not known.

Examination of the opposite ovary at the time of operation reveals atrophy of this organ in less than 50 per cent of the cases. Function was completely restored in all but one case.

2. Hirsutism. Hirsutism was present in 85 per cent of patients with arrhenoblastoma. The hair was usually coarse and distributed over the lower forearms, legs, thighs, chest, chin, and face. At the pubic region it pointed up toward the umbilicus in typical masculine distribution. It is not unusual for the patient to shave every day. Many of the patients demonstrated a temporal recession at the hairline, approaching baldness. The patients who exhibited no hirsutism had no other associated masculinizing symptoms, except for amenorrhea (defeminization). The hirsutism decreases gradually after removal of the tumor.

3. Voice change: This sign was present in 62 per cent of the patients with arrhenoblastoma, some of whom noticed it only in retrospect. The vocal cords, when examined, showed reddening, true hypertrophy, or no change. A prominent Adam's apple appeared in some instances.

After removal of the tumor the voice becomes higher and the vocal cords diminish in size. In some cases no improvement is noted.

4. Atrophy of breast: Seventy per cent of the cases of arrhenoblastoma showed atrophy of the breast. Actual loss of glandular tissue can be determined by careful palpation, even in a breast which is not appreciably diminished in size. This symptom regresses rapidly postoperatively.

5. Hypertrophy of clitoris: Seventy per cent of patients with arrhenoblastoma show clitoral hypertrophy, the clitoris ranging from 2 to 7.2 centimeters in length and averaging about 3 to 4 centimeters. The postoperative regression has not been observed closely. In some cases an appreciable decrease in size has been recorded.

6. Other symptoms: Masculine habitus and muscular development, loss of female fat distribution, acne, and thickening of the skin are frequently noted and mentioned in both groups of tumors. Rare cases of pseudohermaphroditism, vaginal atresia, infantile uterus and adnexa occur.

The prominent masculinizing symptoms of the lipoid cell tumors correspond to the above distribution: amenorrhea was present in all cases except one which was complicated by other hormonal imbalance; hirsutism, 100 per cent; voice change, 90 per cent; hypertrophy of clitoris, 72 per cent; atrophy of breasts, 50 per cent.

Other clinical data. Some writers have stressed the clinical similarity between adrenal rest tumors of the ovary and of adrenal cortical adenomas, hyperplasia, or carcinoma. They would distinguish masculinovoblastoma from arrhenoblastoma on the basis of certain metabolic changes. The presence of moderate polycythemia in 5 cases of masculinovoblastoma has been recorded, some of these associated with bluish complexions. One case of arrhenoblastoma was diagnosed Cushing's disease. It is not remarkable that these findings are present, in view of the interdependence of the pituitary, adrenal, ovaries, and other endocrine glands.

Dorfman, Wilson, and Peters maintain that cortical tumors appear to resemble in all respects arrhenoblastoma and to secrete male sex hormone or an allied substance with the same action. They state, however, that patients with cortical tumors may, in addition, have hypertension and diabetes.

In the present series it is found that hypertension is correlated more obviously with age than with the type of tumor present. Comparison of the blood pressure in the two groups shows that only 2 of 9 cases of masculinizing lipoid cell tumors had a blood pressure over 140/90, while 8 of 20 cases of arrhenoblastoma had a blood pressure of 140/90 or above. Of the latter group the average age was 47 years.

Furthermore, diabetic tendencies are not found exclusively in the lipoid cell group. One case of arrhenoblastoma had glycosuria; another case had elevated blood sugar; and 5 of 6 showed diabetic tendency with the glucose tolerance test. An elevated blood sugar was recorded in none of the cases of masculinovoblastoma, but the glucose tolerance test in 1 case showed a diabetic curve (Fig. 2). A transient glycosuria may be found in both groups of tumors.

Generalization as to metabolic effects cannot be made with the data available and should be deferred until more evidence is at hand.

Other glands may be involved. Hyperplasia of the adrenal glands, a pituitary cyst, and enlarged thyroid glands have been associated with the presence of arrhenoblastoma. The basal metabolic rate varied in the arrhenoblastoma group from −16 to +24; 6 were below normal, averaging −13, and 5 above normal, averaging +24. The basal metabolic rate was recorded in 3 cases of masculinovoblastoma: −7, +19, +39.

Improvement and recurrence. All of the cases show regression of symptoms except those which ultimately prove fatal. Ten to 14 per cent of cases of arrhenoblastoma have shown metastases, and 2 in 17 cases of masculinovoblastoma.

Malignancy may be suspected clinically in the presence of a rapidly growing tumor, ascites or hydrothorax or both, loss of weight, or return of symptoms postoperatively after the first period of initial improvement. The prognosis cannot be determined from the histological appearance of the primary tumor. Indeed, the metastatic lesions may vary widely and may not resemble the original mass. Usually the metastatic lesions are sarcomatous in pattern and may be nonincretory, thus creating some confusion in clinical evaluation of the symptoms unless a careful past history is obtained (Figs. 4, 5, 14, 15*K*).

MORPHOLOGY

1. *The masculinovoblastoma* is a well encapsulated, round or oval tumor, 2 to 16 centimeters in length, averaging 7.1 centimeters. Only 3 cases in the entire series were above average size. The cystic changes found in less than 25 per cent of the cases are correlated with size of tumor. The ovary is compressed to one side of the tumor or may be absent altogether. The yellowish-orange color is due to the presence of lipoids within the cytoplasm of large polyhedral cells. These cells tend to be arranged in columns within a very vascular delicate fibrous stroma. In some areas near the periphery of the tumor the cells may be clumped together. A fine reticulum is usually

present. Ponceau fuchsin stains may show fuchsinophile granules within the cytoplasm of some of the cells, supposedly indicating androgenic function. Some of the tumors show inclusions resembling granulosa cells, spindle-shaped sarcomatous cells, or theca cells.

The variation in appearance of the tumors heretofore reported may be due to the quantity, distribution, and type of fat present.

2. *The arrhenoblastoma* averages 12 to 14 centimeters in its greatest dimension, the cases ranging from 2.5 centimeters to an indeterminate size ("fills pelvis," "large as a man's head," etc.). Thirty per cent of the cases are above average size and most of these show cystic changes. The tumor may be white or yellow, or show hemorrhagic necrotic areas.

a. The adenoma tubulare (testiculare) is said to be the most differentiated form. This tumor is composed of round tubular or gland-like structures of varying size, often filled with pink-staining homogeneous material. The epithelium may be cuboidal or columnar, and there is no marked resemblance to testicular tubules. Some cases reported as struma ovarii bear a striking histologic similarity to this type of arrhenoblastoma. When spindle-shaped cells and interstitial cells are found interspersed with the tubular structures, some masculinization may occur.

b. The intermediate form contains varying proportions of the sarcomatous cells and interstitial cells. Gradations between the two are seen and abortive attempts at tubule formation are frequent. This type is invariably associated with masculinization.

c. The least differentiated type exhibits a sarcomatous pattern resembling ovarian stroma in which are found clumps or columns of polyhedral cells similar to those comprising the masculinovoblastoma. There is very little tubule formation. Masculinization is found in 100 per cent of these cases.

In a small percentage of cases of arrhenoblastoma various teratomatous inclusions have been found: mucous membrane, cartilage, bone, thyroid (adenoma tubulare?), etc. These inclusions have formed the basis for theories as to the teratomatous derivation of arrhenoblastoma.

HISTOGENESIS

Present theories (86, 88) attribute the origin of arrhenoblastoma to certain undifferentiated male directed cells in the rete ovarii, the female homologue of the testis. Masculinovoblastomas are thought by most workers to represent adrenal rests (97); by some, tumors of lutein cells (45).

A histogenetic relationship between the two tumors is suggested by Case 3, in which adrenal-like tissue (tumor nodule *B*) was found associated with typical arrhenoblastoma (tumor nodule *A*). That these 2 masses are variations of one tumor is evidenced by the following facts:

1. The striking superficial resemblance of the interstitial cells of the arrhenoblastoma to those comprising the adrenal-like tissue.

2. The presence of sarcomatous cells and polyhedral cells in other tumor nodules in various proportions. Transitions between the two types of cells are seen.

3. At operation one metastasis was seen which proved to contain masses of lipoid cells, tubular elements, and spindle cells, so that both "primary tumors" were represented in the one metastasis.

4. Finally, cytological studies showed the cells comprising tumor nodule *B* and those termed "interstitial cells" in the arrhenoblastoma to be identical (Table III).

It is of interest that Haffner mentions large masses of interstitial cells in his case of arrhenoblastoma (Table I, Case 6).

If a relationship between these two nodules actually exists, it may be asked how one tumor can be derived from two cell rests. The pre-existing confusion concerning the masculinizing ovarian tumors may justify a reconsideration of the available morphological, clinical, experimental, and embryological evidence for the present theories of histogenesis and a search for a common ancestor for the two types of tumor.

a. Evidence for "adrenal rest" theory. The term "adrenal rest" is not without reasonable basis (83). It is conceivable that these cells may be accidentally misplaced in the neighboring gonads during the course of their embryonic descent into the pelvis from their position near the mesonephros (4, 45, 86, 88).

TABLE III.—CYTOLOGICAL STUDIES: A COMPARISON OF CELLS OF ADRENAL, TESTIS, AND OVARY WITH THOSE COMPRISING VARIOUS MASCULINIZING OVARIAN TUMORS

Tissue	Size cell (microns)	Size nucelus (microns)	Glycogen	Fat (Scharlach red)	Birefringence	Ponceau fuchsin stain	Reticulum	Hematoxylin and eosin stain
Case 3: Cells comprising yellow nodule	Largest: 53.9x23.4 Average: 19.1x17.7	29.2x13.1 6.9x6.2	?	Large and small droplets; fine droplets in stroma	Fine crystals periphery of cell; some extracellular	"Androgen cells" seen?	Fine fibrils circumscribing cells	Cell membrane distinct in less concentrated areas; cytoplasm foamy or granular; clear nuclear membrane; 1 or 2 eccentric nucleoli; granular or coarse eccentric nucleus
Case 3: "Interstitial cells" in white mass	19.0x17.0	7x6	?	Large and small droplets	Same	Same	Same	Same; less variation
Case 3: Spindle cells in white mass	—	12.3x5.4	?	Fine droplets: occasional larger clumps	Rare, granular	Same	Good reticulum	Cell borders not distinct; watery nuclei, elongated, 1–3 nucleoli varying with size of cell; nuclear membrane distinct
Cells comprising masculinovoblastoma	11.5x7.7 to 19x15.4 Average: 17.0x14.3	8.47x7.7	?	Large quantities of intracytoplasmic and extracellular	Frequent, fine and acicular; few large clumps	No androgen cells seen	Very fine and light reticulum	Uniform: cytoplasmic outline distinct when large amounts of fat present; prominent nuclear membrane: 1–2 eccentric nucleoli in coarse round nucleus
Cells from luteinoma	21.6x21	9x9	?					Cytoplasm granular; cells uniform; some distinct nuclear membrane; eccentric nucleolus in round or oval nucleus
Testis: interstitial cell of Leydig	15.4x13.1	6.2x5.4	None	Scarce; large and small droplets in Leydig cells	None	No reaction		Cytoplasm foamy or granular, containing brownish pigment; nucleus fairly compact, slightly oval; chromatin finely dispersed; frequent eccentric nucleolus
Adrenal: cortical cells	9.24x9.3 to 23.4x17 Average: 15.4x15.4	5.39x3.9		Packed in zona fasciculata	Many large clumps crystals in zona fasciculata	No androgen cells seen	Few strands in outer cortex	Morphology varies with position; nuclei vary; wrinkled but distinct nuclear membrane; indistinct small nucleolus; granular clumps of chromatin, or watery nucleus
Corpus luteum: lutein cells	—	10.4x8.9	None	Early; fine droplets Late: marked accumulation	None	None	Scarce reticulum	Cell outlines indistinct; distinct nuclear membrane; watery nucleus; sparse chromatin; 1–2 nucleoli
Corpus luteum: paralutein cells	17.7x16.3	6.6x5.4	Tiny droplets in vascular regions	All phases: marked accumulation, large and small droplets	Rare; fine and acicular	No androgen cells seen	Fine prominent fibrils	Cytoplasm eosinophilic, foamy or granular; polyhedral, moderately well defined cell membrane; eccentric or central nucleolus in granular nucleus
Ovary: paralutein stromal cells	—	11.5x6.2	Occasional accumulation about blood vessels in trabeculae	Fine droplets	None	None	Good reticulum	Spindle shaped; cytoplasm indistinct; large elongated nucleus; 1–3 nucleoli; coarse clumps chromatin

Certainly if they occur in the eye (58) and epididymis (36), they may occur in the ovary. Moreover, morphological evidence supports the adrenal rest theory in that these tumors bear more than a superficial resemblance to the zona fasciculata of the adrenal cortex, both in their tendency to line up in columns and their fat content.

Further evidence is given by Greenblatt and associates, who compare the lipoids in adrenal rest, arrhenoblastoma, and other tumors to the adrenal and corpus luteum. Differential studies of fat content of the masculinovoblastoma group revealed the cells comprising these tumors to be more similar to those of the adrenal cortex and of adrenal cortical adenomas than to those of the corpus luteum.

In our studies (Table III) the lutein cells were found to be more or less uniform and static. They resembled neither the adrenal cortex, masculinovoblastoma, nor interstitial cells of the arrhenoblastoma. Furthermore,

we found little similarity between the latter cells and the Leydig cells of the testis.

In these and other respects our findings agree essentially with those of Greenblatt, with the exception that all of the arrhenoblastomas studied by us had minute fat droplets in the cytoplasm of the sarcomatous cells.

If the choice for the histogenetic relative of the masculinovoblastoma lay between the adrenal rest and the corpus luteum only, the adrenal should be chosen, not only on the basis of fat content, but also on the basis of cytoplasmic and nuclear similarities.

b. Evidence for ovarian origin of masculinizing tumors.

1. Morphological: Our cytological studies pointed very definitely to the striking similarity between the paralutein (or theca lutein) cells of the corpus luteum, the interstitial cells of the arrhenoblastoma, and the cells comprising the tumor nodule *B* of Case 3. The presence of doubly refractile crystals in theca lutein or paralutein cells, the abundance of neutral fats, the reticulum, and the glycogen distribution justify the assumption of its potentialities as a factor in the histogenesis of "lipoid cell tumors" of the ovary.

The presence of glycogen and fuchsinophile granules in the adrenal gland (45, 8) and their occasional presence in tumors designated as masculinovoblastomas have contributed to the theory that the two tissues are related. However, both of these substances are also found at the periphery of the corpus luteum in the paralutein cells.

Reticulum studies may be of help in the future in differentiating between tumors of thecal origin and those of adrenal origin (112) since the theca cells about the follicle and their luteinized cousins around the corpus luteum both contain a more striking reticulum than the adrenal cortex.

2. Functional: Culiner observed, "The similarity of these [theca lutein] cells to the adrenal cortex is remarkable and is probably not without significance." Therefore, it is pertinent to determine the functional basis for the incrimination of theca lutein cells in the histogenesis of masculinovoblastoma.

This relationship was suggested by Novak in 1940 (86): "The endocrine significance of these theca lutein or paralutein cells is not known, but their appearance would seem to leave little doubt that they play an endocrine rôle of some sort."

It is well known that preovulatory secretory changes can be recognized in the endometrium indicating a source of progesterone other than mature lutein cells of the corpus luteum. This finding is associated with the appearance of luteinized theca interna in the ovary.

Furthermore, the androgenic effect of progesterone has been demonstrated (51, 99) by the fact that progesterone, when given to castrated male rats, will maintain the prostate, and, when given to the immature female in large doses, will cause clitoral hypertrophy.

In recent years evidence has accumulated for the presence of other androgenic substances in the ovary and the involvement of the paralutein or theca lutein cells in their production (26). Greene, Burrill, and Ivy (51) have shown that APL will stimulate clitoral hypertrophy in the guinea pig, as well as the rat, an effect not obtained when the ovaries are removed. Greene (99) has shown that APL at the same time produces increased numbers of interstitial cells (luteinized theca cells) in the mouse ovary and causes a marked growth of the clitoris. Ovaries transplanted to the ears of male rats will maintain the prostate and seminal vesicles for a variable period of time.

Therefore morphological similarities of the paralutein cell to the adrenal cortex and to the interstitial cells of Leydig (more superficial in the latter case) are supported by experimental evidence that androgens are produced in the ovary and more specifically by the paralutein or theca lutein cells.

3. Chemical: The correlation is further strengthened by chemical tests which show a rise in phospholipids and cholesterol esters in ovaries during the middle part of the cycle when luteinization of theca interna and formation of theca lutein cells is taking place (112). Not only is a higher concentration of these substances found in the incretory group of ovarian tumors than in the nonincretory group, but a further increase was found associated with luteinization of granulosa or theca cell tumor (57). This corresponds to our

polariscopic studies which demonstrate birefractile substances, not only in the adrenal cortex, but also in luteinized theca cell tumors, "interstitial cells" of the arrhenoblastoma, masculinovoblastoma, and the theca lutein cells around the corpus luteum.

4. Clinical: There is abundant clinical evidence that the recently discovered androgenic action of the ovary is directly related to the presence of theca lutein or paralutein cells. Stein and associates, in 1935 and 1939 described the presence of luteinized theca interna of multifollicular cysts in 28 cases of amenorrhea (106, 107).

Other instances are recorded, including Turner's case in which multiple cystic ovaries were found in a case of hirsutism and amenorrhea (114). The symptoms regressed when the ovaries were partially resected. The ovaries showed luteinization of the theca interna and some luteinization of the ovarian stroma.

In the case of Saphir and Parker, previously classified as masculinovoblastoma (Table II), the virilizing symptoms were associated not with tumor but with luteinized follicles and an accumulation of cells resembling theca lutein cells. That these changes are due to luteinization, and not to fatty degeneration, can be adequately determined by Traut, Kuder, and Cadden's criteria of (a) well defined nucleus, (b) size of cell, (c) enlargement and fragmentation of Golgi bodies, (d) shortening and disappearance of rods (112).

Reis and Saphir's case, also classified as "adrenal rest," (Table II), contained a tumor-like nodule 2.9 centimeters in diameter, which was thought to be corpus luteum. "In one corner, however, there was an accumulation of very lightly stained cells. These were definitely smaller than the cells making up the corpus luteum and had an eccentrically situated vesicular nucleus. Some of the cells showed an empty cytoplasm, while in others the cytoplasm was light pink. They differ morphologically from lutein cells, although it is possible that these cells are lutein cells" (or theca lutein?).

Case 1 of Rottino and McGrath (Table II) had a recurrence of hirsutism and amenorrhea 4 years after the removal of the tumor. The opposite ovary was shown to contain 8 thin walled theca lutein cysts. It is curious that the original masculinizing symptoms should be caused by "adrenal cortical cells" and the recurrence of symptoms by cells of ovarian origin.

The evidence for the identity of "virilizing lipoid cells" with theca lutein cells may be strengthened by the examination of plates and reading the descriptions of other cases of masculinovoblastoma.

It has been shown that the tumors of the arrhenoblastoma and masculinovoblastoma types contain cells which morphologically resemble the paralutein cells or the theca lutein cells of the normal ovary as much as they resemble adrenal cortical cells; experimental evidence has been cited to show that these cells are capable of producing androgens. It has been shown that masculinization without tumor formation is associated with accumulations of these cells, and masculinization with tumor formation is associated with cells that in all respects are similar to theca lutein cells.

5. Embryological and developmental: a. Granulosa and theca interna cells are derived from the primitive ovarian mesenchyme in the embryo. Tubular structures are seen in both female and male gonads below 15 millimeters (4, 41, 85).

The ovary is derived from the proliferation of celomic epithelium just anterior to the mesonephros. At about 5 millimeters the embryonic gonad consists of a surface layer of superficial cells and of mesenchyme in which begin to appear radially arranged cell cords. The connective tissue surrounding the cell cords is derived from the mesenchyme. Recent evidence points also to the derivation of the cell cords from the mesenchyme, rather than from invagination of the surface epithelium, as was formerly supposed (41). Up to about 15 millimeters the male and female gonads are quite similar, although their eventual sex differentiation has long been predetermined (85). After this indifferent stage, the cell cords in the males form the tubular system of the testis, and those of the female give way to the follicle (granulosa and theca interna cells). Novak (88) agrees that the theca cells come from the ovarian mesenchyme.

b. In the adult ovary, theca lutein or paralutein cells are normally derived from (1) luteinization of theca interna of the maturing follicle and subsequent continuation of this process as the corpus luteum is formed, and (2) from ovarian stroma.

It has been shown that the "interstitial cell" (theca lutein) is differentiated from the stroma in lower animals and luteinization of ovarian stroma can occur in adult female ovaries, producing similar appearing cells. Greenblatt also identifies the interstitial cells of the stroma with theca lutein cells (49). In Rottino and McGrath's case (98) this finding was associated with hirsutism and amenorrhea, which further demonstrates the androgenic action of these lipoid cells, whether differentiated from stroma or from theca interna already present.

Culiner's excellent descriptions (26) also show the concomitant differentiation of stroma cells and luteinization of the theca interna. In fact, sometimes the latter merges with the stroma, producing isolated islands of theca lutein cells which are seen grossly as yellow specks on the cut surface.

c. Ovarian tumors containing tubular structures and lipoid cells may be produced by the radiation of mouse ovaries.

Traut and Butterworth (111) show the development of granulosa cell tumors and luteomas by this means. Geist, Gaines, and Pollack's descriptions up to the point of tumor formation correspond with Culiner's observation in the human (39). First the follicle is destroyed; this is followed by proliferation of the theca, which merges with surrounding parenchyma; the stroma cells increase in size, become round, and separate in groups or cords (compare arrangement of "adrenal rest tumor"); luteinization of the theca cells and differentiation of parenchymal cells follows. It is interesting that the corpora lutea are well preserved throughout, a finding which justifies its rejection as a potential factor in tumor production.

After 6 months 2 types of tumors are formed: the luteinized functional tumor and the nonfunctioning adenoma caused by invagination of the surface epithelium. Mixtures of both types occur.

c. Previous problems leading to confusion in literature. The histopathology of the various functional tumors is better understood if the above findings showing the relation between them and the ovary are accepted. The following observations which have previously complicated the histogenetic classification of masculinizing ovarian tumors may be explained:

1. The sarcomatous appearance and the spindle cells which comprise the more undifferentiated type, not only of arrhenoblastoma, but also of granulosa and theca cell tumors.

2. The gradation of spindle cells to interstitial cells in the arrhenoblastoma.

3. The oft quoted "enigma" that the most differentiated type of arrhenoblastoma, the adenoma tubulare, has no masculinizing effect, while the least differentiated has the most masculinizing effect. We agree with Norris that the adenoma tubulare does not resemble testis. If present embryological and experimental evidence be applied to this group, the tubules may represent simply a nonfunctioning adenoma such as produced by Geist and associates, with no histogenetic connection to the testis or to the cells forming the functional part of the tumor; or the tubules in arrhenoblastoma may actually be a reflection of their primitive condition as sex cords, elements as characteristic of the female gonad as the male.

It is impossible to grade the three types of arrhenoblastoma accurately; when this is attempted, there is seen to be no correlation between primitivity and degree of masculinity. In our opinion the androgens are produced by the polyhedral cells in all forms of arrhenoblastoma, as well as masculinovoblastoma, or by gradations between the primitive stroma and these cells.

4. Difficulty in strict classification of the functional group of ovarian tumors. Gradations between all types are seen. Banner and Dockerty show that some granulosa cells are included in their series of theca cell tumors. Novak says that the two groups no longer can be easily separated. He further states that partial or complete luteinization of granulosa cell tumors (and, more important, theca cell tumors) may occur to produce masculinizing lipoid cell tumors.

Such a patient was recently seen in this laboratory. In this case complete masculinization occurred in a 19 year old girl. The tumor was 7 centimeters in length, well circumscribed, and bright orange. Microscopically cylindroid strands of granulosa cells were noted, masses of theca cells, and the expected large percentage of lipoid cells (Fig. 15 *J*).

Plate (94) and Mechler and Black review cases of gynandroblastoma which are merely arrhenoblastomas containing granulosa cells. Case 3 illustrates the completion of the cycle, the transition between arrhenoblastomas and masculinovoblastoma.

The observations described are summarized in Figure 15, and the interrelationship of the functional group of ovarian tumors is shown.

SUMMARY

1. Three case reports of arrhenoblastoma are presented: 1 with a 10 year follow-up showing no recurrence; 1 with metastases to liver, appendix, tubes, and peritoneum, and a clinical picture of Meig's syndrome; 1 which also contained adrenal-like tissue.

2. Evidence is presented to show a possible relationship between arrhenoblastoma and "virilizing lipoid cell tumors" (masculinovoblastoma, hypernephroma, adrenal rest) of the ovary. The case quoted demonstrates both types of tissue in intimate association, one metastasis with cells common to both tumors, and cytological studies identifying the cells of the adrenal-like tissue as the so called interstitial cells which are found in arrhenoblastomas.

3. The total number of cases of arrhenoblastoma are reviewed, with a discussion of the outstanding clinical and pathologic features. These are compared to a similar outline of the cases of masculinovoblastoma to show clinical similarities and dissimilarities. Data are presented to show the frequency of metabolic changes in arrhenoblastoma and masculinovoblastoma, previously considered to be a differential clinical feature.

4. The histogenesis of the masculinovoblastoma and arrhenoblastoma groups of ovarian tumors is discussed in detail. The embryology is reviewed to show that the ovary is capable of producing both types of tumor. Morphological studies demonstrate the similarity between the polyhedral lipoid containing cells in both types of tumor and the paralutein or theca lutein cells of the normal ovary. Clinical, functional, and experimental evidence is cited to support this relationship. It is concluded that theca lutein or paralutein cells are directly related histogenetically to both groups of masculinizing tumors. This obviates the necessity of the adrenal rest theory as an explanation of the histogenesis of masculinovoblastoma or "virilizing lipoid cell tumor."

5. It is suggested that the cells comprising arrhenoblastoma are related as follows to ovarian structures: the spindle cells, forming tumors of sarcomatous pattern, represent totipotential ovarian stroma; the tubular structures are related to invaginated surface epithelium or to primitive sex cords of the female gonad; the "interstitial cell of Leydig" in arrhenoblastoma simulates the paralutein or theca lutein cell. The virilizing lipoid cell tumor in its pure form may represent a neoplasm of luteinized theca interna cells or of paralutein cells and morphologically is more properly termed "paraluteinome." All types of functional tumors probably originate from undifferentiated mesenchyme.

6. A diagram illustrating the interrelationship of functioning ovarian tumors is presented.

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THE TECHNIQUE OF THYROIDECTOMY

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DURING many years of experience with thyroidectomy, we have constantly made changes in our technique. For this reason a description of our present technique, accompanied by the reasons for its various steps, may be of interest. We claim no originality for any of our steps, as most of them are the result of trial and error after observation of other surgeons in various clinics of the world.

Teamwork is especially important in this operation. Our team, consisting of surgeon, assistant surgeon, anesthetist, and instrument nurse, has remained almost intact for many years. Our internes and residents get their experience as second assistants. To have a well trained and experienced assistant surgeon is like having an extra pair of hands because they act and anticipate your wants as though they were being directed by your own brain. A competent anesthetist who takes an interest in thyroid cases and becomes familiar with each patient before operation makes it possible for the surgeon to dismiss from his mind any concern about the patient's condition unless warned by the anesthetist. We depend almost entirely on the judgment of the anesthetist as to whether to do a one stage or two stage operation. An instrument nurse of your own, who assists at all operations, looks after the preparations in the operating room, sees that the proper instrument or suture is ready when wanted, relieves the surgeon of much anxiety and allows him to keep his eyes focused on the wound at all times. The instruments, too, should be the private property of the surgeon, should be uniform, should not be used for any other operation, and should be kept in good working condition. For hemostasis, we use the Rankin hemostats throughout.

Our anesthetic of choice is cyclopropane. In patients with heart disturbance, especially those that are fibrillating, ether and oxygen, pentothal intravenously, or local anesthesia is used. When there are pressure symptoms, especially respiratory difficulties, an intratracheal tube is introduced, either through the nose or by direct laryngoscopy through the mouth.

Only the immediate preoperative and postoperative treatment will be described in this paper. The night before operation the patient is given an average dose of 3 grains of luminal. This is repeated 3 hours before the operation. A hypodermic of morphine, grain $\frac{1}{6}$, and atropine, grain $\frac{1}{150}$, is given $\frac{1}{2}$ hour before operation. The patient is visited by the surgeon on the latter's arrival at the hospital on the day of operation to be sure no contraindication to operation has developed. No other visitors are allowed, the room is left dark, and the patient is not disturbed. All preparations are made the day before operation. The patient is preferably given a room on the same floor as the operating room and at the appointed time is placed directly on the operating table in her room and transported to the operating room as gently as possible.

The operating room is prepared and the anesthetist and surgeons are ready before the arrival of the patient. When the patient arrives, she is immediately, though without haste, anesthetized, to prevent her from seeing much of the operating room or hearing any of its noises. There should be no unnecessary noise or talking in the operating room.

As soon as the patient is unconscious, her arms are fastened to the sides of her body by winding the drawsheet around them, a sandbag is placed under her shoulders to hyperextend the head and push the thyroid forward, the upper half of the table is raised about 30 degrees and the ether screen placed in position (Fig. 1). The operative area is then wiped with ether to remove all fat and sebaceous material from the skin and this is followed by a not too wet application of half strength tincture of iodine. We have never seen any reason for changing to any other antiseptic.

From the Surgical Service of the Deaconess Hospital, Buffalo, N. Y., and the Surgical Department of the University of Buffalo Medical School.

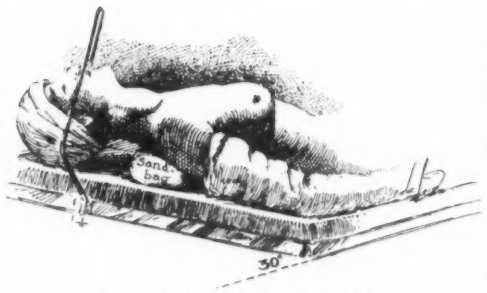

Fig. 1. Position of patient on table.

Serious blistering of the skin almost never occurs and infection of the wound is almost unknown, about twice in the last thousand cases.

We have tried to make the draping of the patient simple, without moving any part of the patient or using special sheets, but nevertheless efficient, and we believe we have succeeded. A crumpled sterile towel is placed in the hollow on each side of the neck. A towel is placed across the upper part of the chest and still another placed a little higher over this, its upper edge kept taut and fastened on each side of the neck to the crumpled towel and the skin near the upper edge of the operative area with a towel clip and then turned up and fastened to the ether screen with another towel clip on each end. Folded towels are placed diagonally over each side of the neck, overlapping below in the midline. A laparotomy sheet is placed over the patient with the operative area appearing in the opening. Finally, several crumpled sponges are tucked into any potential openings on each side to cover them and to anchor the draping into position (Fig. 2, a, b, c, and d).

The incision is outlined with the back of the knife about 1 inch above the suprasternal notch and parallel to the folds of the neck. Thus it is made slightly curved with the convexity downward. Whenever there is much protuberance of the skin caused by the underlying goiter, the incision is placed correspondingly higher so that after the goiter is removed it is still about 1 inch above the suprasternal notch where it can easily be covered by a string of beads until it fades and becomes almost invisible. A scar that lies on the sternum is very unsightly and difficult to cover.

The incision is made through the skin, subcutaneous tissue, and platysma to the plane of cleavage just above the cervical fascia, avoiding the anterior and external jugular veins that lie on this fascia. If they are injured, they are easily clamped and tied, preferably with a surrounding suture, but usually they are not injured.

The upper flap is then developed partly by sharp dissection and partly by gently wiping it upward with a sponge. This latter maneuver saves time and locates the bleeding points more definitely, thus saving the number of hemostats used. The lower flap is similarly prepared. All bleeding points are tied with No. 000 chromicized catgut. A towel is attached to the edge of the lower flap to cover the skin and the flaps held apart by a self-retaining Crotti retractor (Fig. 2, e and f).

We use chromicized catgut throughout. We are well aware of the arguments in favor of nonabsorbable suture material, but feel that by using very fine catgut, No. 000 for superficial ties, No. 00 for the rest of the operation, we do not cause much more irritation than is caused by nonabsorbable material and without the risk of sinus formation, such as we have observed when the latter was used. It is true that these fine ligatures break if too much force is used, but with practice the amount of tension allowed is soon learned and the occasional tear is taken philosophically as the price to be paid for using fine catgut. When such a ligature is once properly tied without tearing, it is just as secure as a silk or cotton tie.

A short vertical incision is now made in the midline through the fascia down to the surface of the gland. After a scissors is inserted upward and downward in this plane and the tissues are separated from the gland, the incision is extended upward to the base of the upper flap and downward to the sternum.

The right ribbon muscles are dissected from the gland and retracted with a Parker retractor. The right lobe is grasped with a Lahey forceps and gently pulled upward, at the same time it is gently separated from its surrounding tissues by inserting a finger. This latter must be done very carefully to avoid tearing the veins, especially the middle thy-

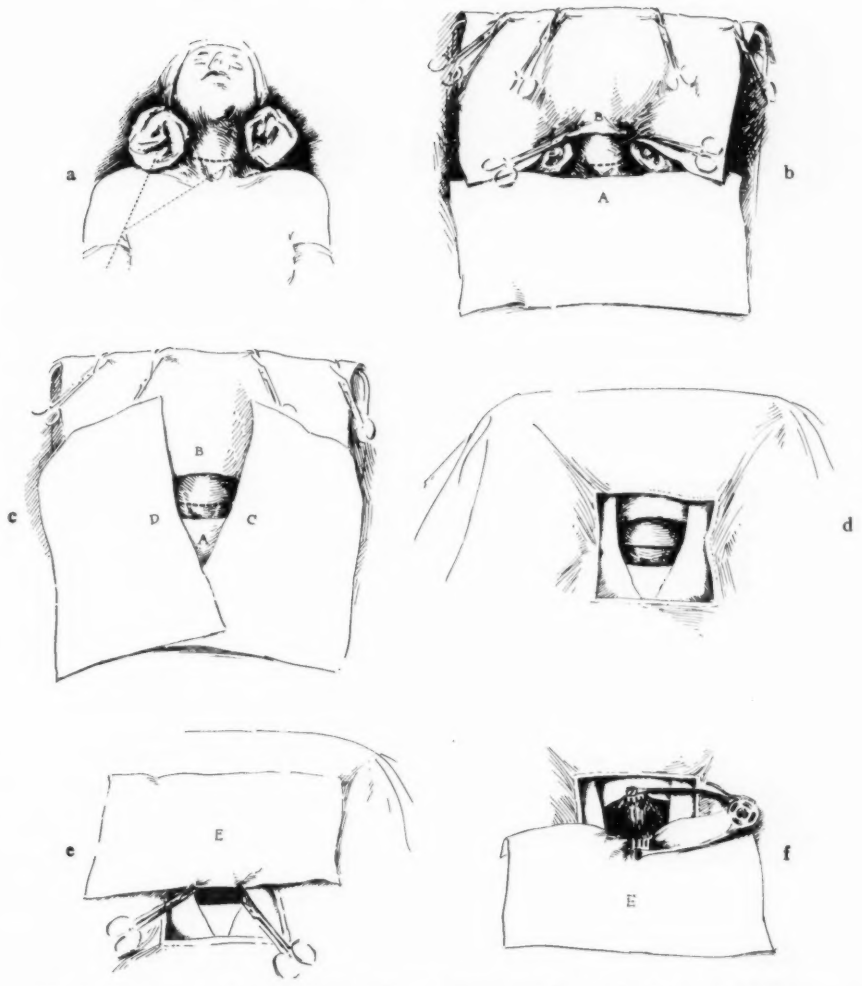

Fig. 2. Draping of patient. a, Crumpled towels placed at sides of neck. b, Towel *A* laid across chest; *B* clamped to skin and crumpled towels. c, Towels *C* and *D* placed. d, Laparotomy sheet placed; incision made. e, Edge of towel clipped to lower edge of incision. f, Free edge of towel *E* turned downward; retractor placed.

roid vein. As soon as this vein appears, it is doubly clamped and divided. This vein emerges from the true fascia of the gland and by dividing it, the lobe is further liberated.

If, on inserting the finger, the goiter is found to be very large, to extend into the chest or behind the trachea, or to be unusually adherent, it is not delivered until the ribbon muscles are divided. In such a case, the sternomastoid muscle is liberated by a diagonal incision through its fascia at its anterior border and retracted out of the way, after which the ribbon muscles are divided transversely between two Kocher clamps and held out of the way with Lahey forceps. This procedure we have found necessary in only

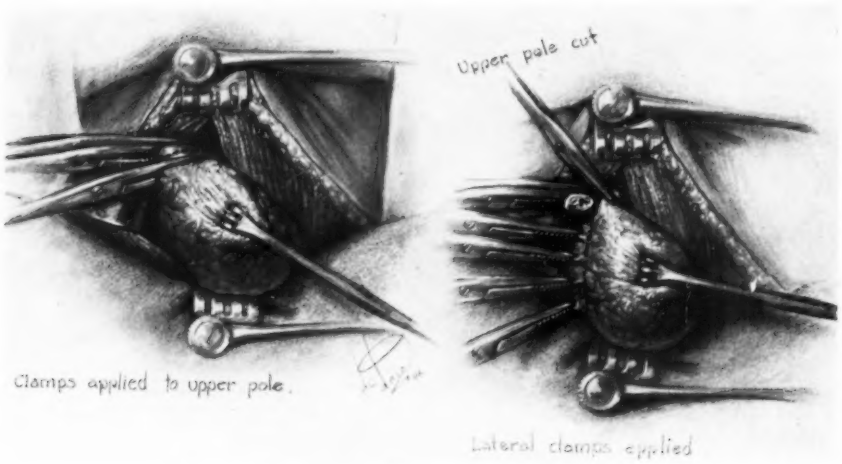

Fig. 3, left. Treatment of superior pole.
Fig. 4. Pole divided, lobe delivered, row of clamps applied.

about 10 per cent of our patients, but when any difficulty is expected the greater exposure obtained is an added safeguard.

After the right lobe is delivered, the superior pole is prepared by traction downward of that part of the gland, retraction of surrounding tissues, and wiping away any extraneous tissue with a "wiper" (a small folded piece of gauze in a hemostat). Three hemostats are placed on the superior pole just above the gland and the pole divided between the lower two (Fig. 3). Thus the gland is further liberated and it is possible to hold it well over to the left, so that its entire lateral surface is exposed. In cases in which the lobe extends above the line of easy exposure or behind the trachea, the individual vessels at the superior pole are clamped and divided, and the upper part of the lobe allowed to roll out.

At this point it is necessary to decide how much of the lobe to leave behind. This depends upon the age of the patient, the type and toxicity of the goiter, and its conformation. We aim to remove all adenomas completely, even if they extend far back into the area where the recurrent nerve and parathyroid glands are situated. But in this case the hemostats are placed so close to the tumor that the posterior capsule is left. In general, we leave a thin layer of gland tissue as well. Hemostats are placed along the line of contemplated incision and short cuts made above each hemostat (Fig. 4). The recurrent nerve is not visualized as a routine, but only when we think it is indicated. We believe that there is more danger of injuring the nerve when it is exposed by dissection than there is when its normal location is avoided.

After the outer edge of the lobe is thus mobilized, the isthmus is divided between clamps and the remaining attachments of the right lobe are divided by placing hemostats on the median aspect close to the trachea and working to the right until the lobe is free. All vessels are tied with No. 00 chromegut. At the superior pole, however, a suture is placed around the vessels above the two hemostats, tied, the upper hemostat removed, and another tie made around the lower hemostat.

One side is completed before beginning the other side, so that the operation may be terminated at this point, if necessary. After all bleeding is controlled on the right side, a loose tampon is placed in the hollow left by the gland. Enough dissection is made of the left lobe to determine whether operation is necessary on that side. If so, the surgeon repeats the same performance on the left side.

If there is difficulty in controlling the oozing from one of the stumps, the lateral border is

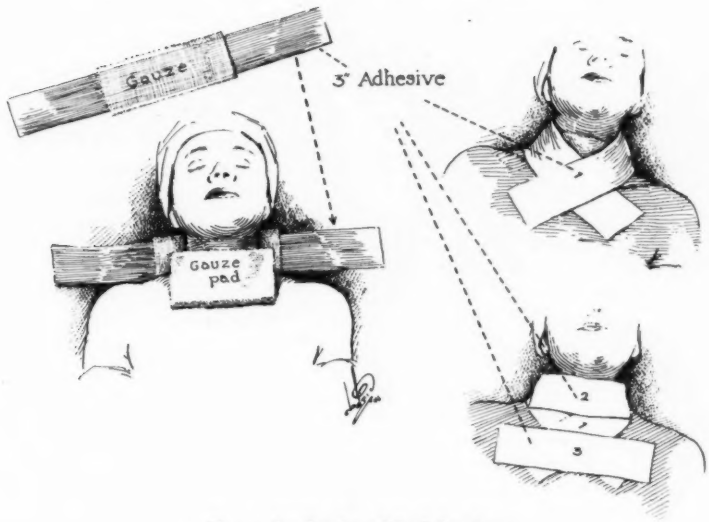

Fig. 5. Application of final dressing.

sewed to the pretracheal fascia to fold the raw edge over on itself and thus control the oozing. If the field is dry, this procedure is not carried out because the raw area is eventually covered by the ribbon muscles and because there is a slight danger of pulling on the recurrent nerve, as indicated in a previous paper (1).

The pillow under the shoulders is now removed and the cavity on each side irrigated with a normal saline solution. Thus blood clots are washed out, any residual bleeding is uncovered, and any possible infection is washed out or diluted.

If the ribbon muscles have been divided transversely, they are sutured with a running lock stitch. The ribbon muscles are now brought together in the midline in two layers with a running suture, first taking in the muscles only and returning as a fascial suture. This makes a good covering for the thyroid stumps and also for the exposed trachea, preventing attachment of the overlying tissues.

The incision in the skin and platysma is closed with Michel clamps, care being taken to evert the edges so that the divided edges of the platysma muscle are closely approximated and good healing takes place. If this does not occur, the platysma tends to pull the scar apart and widen it. We have found by experience that Michel clamps alone cause better healing and a finer scar than sewing the tissues in various layers, besides saving considerable time.

A fairly large dressing is placed over the wound and held in place by a long wide strip of adhesive plaster going around the neck and crossing over the dressing in front. Shorter strips of adhesive are placed over the upper and lower borders of the dressing (Fig. 5).

We seldom drain the wounds, even in large intrathoracic goiters. We find that the cavities left are quickly eliminated by pressure from the surrounding tissues. Occasionally we encounter collections of serum under the skin, but these can easily be aspirated. The exceptions are cases of uncontrollable oozing or of known or suspected infection. This belief has been a gradual process until we are convinced that the placing of a drain is not only unnecessary but sometimes even invites infection and prevents a perfect scar.

In bad risk cases, the operation is done in several stages. In such cases we may merely make the incision or may do one side only. Whenever we are in doubt as to the advisability of continuing the operation, we always play safe and terminate the operation. Thus an opportunity is given to gauge the reaction

of the patient. At the subsequent operation, the incision is quickly and easily opened and the operation completed. However, we find it necessary to do stage operations in only about 5 per cent of all thyroidectomies. This we attribute to better preoperative preparation.

A word about intrathoracic goiters. It is very easy to miss even a large downward extension of an adenomatous goiter. We have missed some and have operated upon a considerable number left by other surgeons. This possibility should be thoroughly investigated in every case.

As all the circulation of the intrathoracic portion comes from the regular supply of the thyroid, this should be controlled first. The finger is then gently inserted and swept around the tumor. Care must be taken to be in the correct plane of cleavage. Fortunately there are seldom any dense adhesions to the surrounding tissues and we have never had any trouble from that source. The tumor is now slowly delivered by traction from above and pressure of the finger below. The finger is better than an instrument because it is more easily guided and kept in the right place. If the tumor is too large to be delivered in this way, an incision is made in the presenting part of the tumor and its contents, usually colloid in character, partly expressed. This procedure decreases its size so that it can easily be delivered. Its pedicle is then clamped and divided and the tumor removed.

We no longer aim at high speed in operating, but rather to operate gently without any lost motion or unnecessary delays. In this way we operate more safely and almost as fast as when we try to speed up the operation.

The patient is returned to her room, placed in a semi-sitting position for a few hours, and given enough morphine to control restlessness. Water by mouth is encouraged from the start and usually no intravenous fluids are given. If patients are prepared properly, especially if they are given plenty of water and fruit juices preoperatively, intravenous therapy is seldom necessary. The patient is kept as quiet as possible with a minimum of fussing. These patients usually get along better on floor service supervised by nurses experienced in thyroid patients than by entrusting them to inexperienced or meddlesome special nurses.

The initial bulky dressing is changed to a very light one on the day after operation. One-half the clips are removed on the second day and the rest on the third day. Most patients get out of bed on the fourth day and leave the hospital on the fifth day.

Our mortality under this regimen has been 1.2 per cent in our last 1,000 cases. We have had no cases of tetany and no bilateral nerve injuries in these 1,000 cases. With modern methods of preparing iodine-resistant bad risk patients with one of the thiouracil group of drugs or even of curing some of them without operation, we hope still further to reduce our mortality.

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RESECTION OF THE CLAVICLE

With Particular Reference to the Use of Bone Chips in the Periosteal Bed

HARRIS B. SHUMACKER, Jr., M.D., New Haven, Connecticut

IN order to provide adequate exposure of the subclavian and innominate vessels, particularly in operations upon aneurysms and arteriovenous fistulas, resection of a portion of the clavicle is often necessary. I do not know who first employed this procedure. Certainly Cooper in 1859 resected the sternal end of the clavicle and a part of the manubrium in approaching an aneurysm involving the bifurcation of the innominate, as did Burrell in 1895. In 1892 Halsted excised the inner third of the clavicle in extirpating a large subclavioaxillary aneurysm. Before 1886 Bardenhauer had utilized resection of the inner portion of the clavicle and a part of the manubrium and of the first two ribs in operating for a number of conditions, including one case in which a tumor involved the first portion of the left subclavian vessels. Through the years it has become increasingly apparent that added safety could be secured in such cases by removal of some of the bony structures overlying the great vessels.

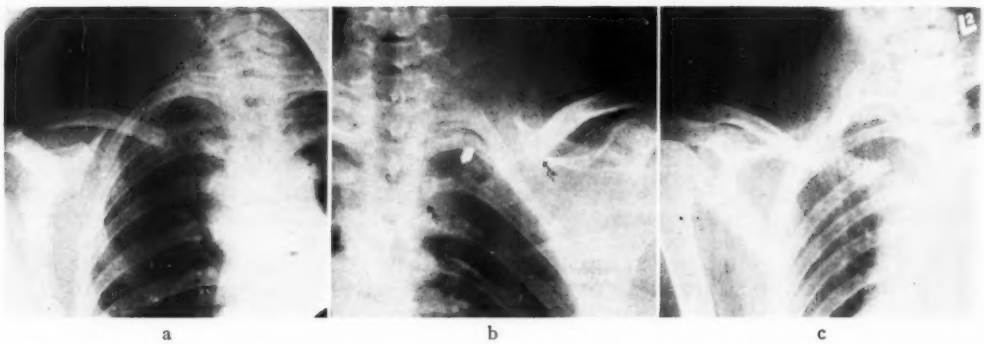
The manner in which the bony defect has been handled has varied. In many of the early cases the excised portion of clavicle was not replaced. Some surgeons have reinserted the bone and fixed it *in situ* by approximating it to the remaining bone with wire or other sutures. The replacement and fixation with sutures of the resected segment of clavicle is subject to many difficulties. Proper immobilization is often not secured and painful nonunions and malunions occur so commonly as to make the procedure eminently unsatisfactory. Holman recently pointed out that the results of subperiosteal resection and discarding of the segment are excellent. My experience is in complete agreement (6).

From the Vascular Center, Mayo General Hospital, Galesburg, Illinois, and The Johns Hopkins Hospital, Baltimore, Maryland.

If the clavicular bed is carefully closed by approximating the periosteum, and if the patient is kept flat in bed for 2 weeks with the shoulders held well back and is encouraged to spend a considerable part of the third week lying on his back, the results are most satisfactory. Firmness rapidly appears in the region of the missing segment so that long before any evidence of osseous regeneration is evident from roentgenological examination, one can hardly tell by palpation that a bony defect exists. Such patients have normal configuration of the chest and shoulders and normal movements of the upper extremities, and are entirely comfortable.

In contrast, it has been my experience that replacement of the clavicle often has most unsatisfactory results. In a single instance in which I returned the segment to its bed and fixed it to the remaining ends of the clavicle with wire sutures, a painful nonunion occurred which was relieved only by excision of the segment. A number of other patients who have come under my care after having undergone replacement of a portion of clavicle following excision during the course of operations for aneurysm have had difficulties such as painful nonunion or malunion, conspicuous displacement of fragments, osteomyelitis, and poor function.

Satisfactory as are the results from discarding of the resected clavicle and accurate approximation of the periosteal edges, it is evident that in many cases regeneration of the bone is slow. Though most of the patients are asymptomatic prior to restoration of bony continuity, some have slight discomfort during heavy lifting and other vigorous exercise. Furthermore, it seemed desirable if it could be accomplished without significant risk or difficulty, to hasten the process of bony regenera-



a b c

Fig. 1. Roentgenograms taken 3 weeks after operation in cases in which bone chips were placed in the periosteal bed. The bone chips are seen. Examination of the x-ray films themselves reveals definite callus formation in cases which are portrayed in b and c, though this is not evident in the reproductions.

tion. With this in mind a small group of patients were treated by filling the periosteal bed with bone chips secured from the excised segment of clavicle. It is the purpose of this communication to draw attention to this procedure.

The operation was carried out upon 4 patients. In 1 patient resection of the middle third of the clavicle was performed, while in 3, resection of the inner third or half of the clavicle with disarticulation at the sternoclavicular joint was done. In 2 of the latter the sternum was split down to the second interspace. One patient had an arteriovenous fistula of the third portion of the subclavian vessels, 1 a mediastinal fistula between the left subclavian artery and vein, 1 a fistula of the second portion of the right subclavian vessels, and 1 an arteriovenous and saccular aneurysm in the anterior mediastinum involving the arch of the aorta and the innominate and subclavian vessels which at operation was found to be inoperable. In each case the clavicle was excised subperiosteally, care being taken to preserve the periosteum intact. In 1 case the periosteum was also transected in order to facilitate exposure. The bone was divided with a Gigli saw. The excised segment was covered with sterile normal salt solution. After the vascular surgery was completed, the removed clavicle was converted into small bone chips 2 to 3 millimeters in diameter with a rongeur. These were packed into the periosteal bed and the periosteum was closed over them with interrupted sutures of fine silk. Ordinarily, sufficient bone chips could be obtained from a half or two thirds of the resected clavicle. The soft tissues were then approximated in the usual manner with interrupted silk sutures. It should be pointed out that in 1 instance the excised clavicle was inadvertently dropped on the floor and was converted into chips after being autoclaved.

The patients were kept in bed for 2 weeks. For the most part they were asked to lie flat on their backs with the shoulders held well back, although they were allowed to assume other positions occasionally after the first few days. No external immobilization was used. During the third week they were allowed to get up but were encouraged to rest a considerable part of the time on their backs. Definite firmness was noted in the region of the resected clavicle even sooner than was the case in patients who had undergone similar resections without replacement of bone chips.

Osseous regeneration was rapid and complete. Three of the patients were examined 3 weeks after operation (Fig. 1). In 2 of them there was already some evidence of callus formation at this early date. One was examined 7 weeks after operation and showed progressing union (Fig. 2a). In another there was evidence of good regeneration 11 weeks after operation (Fig. 2b). Complete regeneration was apparent in the remaining 2 patients who were examined 16 and 18 weeks after operation (Figs. 2c and 2d).

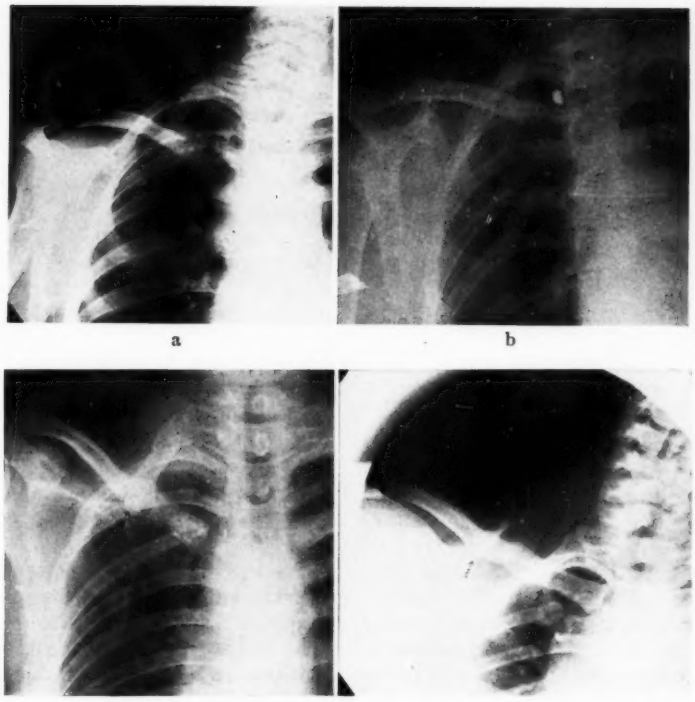


Fig. 2. Roentgenograms taken, a, 7, b, 11, c, 16, and d, 18 weeks after operations in cases in which bone chips were placed in the periosteal bed. It is apparent that excellent bone regeneration is occurring in a and that regeneration is complete in the other 3 cases.

In contrast are the results of roentgenological examination in 10 other patients in whom subperiosteal resection without the use of bone chips had been carried out. In 6 patients there was no evidence of bony regeneration on the last examination, made 5, 6, 7, 10, 10, and 13 weeks after operation. One showed only a small amount of callus formation 27 weeks postoperatively. Another had evidence of a little callus at each end of the remaining clavicle 4 weeks after resection, but had not achieved union 34 weeks after operation, at which time it appeared that the ends of the bone were becoming eburnated. One patient exhibited excellent regeneration in 8 weeks (Fig. 3a). In 1 there was evidence of progressive union 12 weeks after operation and excellent union 29 weeks after operation (Figs. 3b and c). Thus when these patients were examined at intervals of from 5 to 34 weeks after excision, the majority showed no callus formation. Furthermore, when regeneration occurred it sometimes proceeded from the ends of the remaining bone rather than throughout the periosteal bed as was the case with those in whom bone chips were used. In one such case it appeared that union would not be achieved because of eburnation of the bone ends (34 weeks after operation), while another proceeded to excellent bony union (Fig. 3c).

DISCUSSION

In many operations in the clavicular area and in the anterior mediastinum, essential exposure is facilitated by clavicular resection. This is particularly true in cases of aneurysm and arteriovenous fistula of the subclavian, innominate, and internal mammary vessels.

a b c

Fig. 3. Roentgenograms of 2 patients in whom there was good bony regeneration following excision of a portion of clavicle with simple closure of the periosteum: a, taken 8 weeks after operation shows excellent regeneration; b, taken 12 weeks after operation upon another patient shows good regeneration of bone but incomplete union in the mid-portion of the area from which bone was removed. In c, union is seen to be complete 29 weeks after operation.

Frequently section or resection of the clavicle is necessary in explorations of the brachial plexus. In the latter cases simple osteotomy often suffices and excision of a segment of clavicle is unnecessary in order to secure adequate exposure. Although I have had little experience with clavicular section for exploration of the brachial plexus, I have seen many patients who have undergone such procedures. It is my impression that difficulties with maintenance of position of the fragments with various methods of wire and screw fixation are sufficiently common to justify inquiry, at least, into the advisability of resection of a segment of clavicle instead.

When a portion of clavicle is excised the incidence of difficulties in maintaining position, in securing union, and in avoiding pain following reinsertion of the intact segment and fixing it in place with wire sutures is so high as to make its use unwise. Although resection and discarding of the excised segment of clavicle with periosteal closure give excellent cosmetic results, stability, and good function at least for all but strenuous work and exercise, in many instances bony union is long delayed. My own patients have not been followed long enough to permit me to say what percentage will eventually obtain good osseous union, nor are such data available in the literature. In spite of the excellent functional results from such operations it is believed that the simple procedure of replacement of bone chips in the periosteal bed is worth while. From the small group of cases so treated it appears that such operations are followed by good cosmetic and functional results and by rapid and complete bony restoration.

The successful use of bone chips in the periosteal bed in these cases brings up the question of application of this principle in other situations where bone must be excised in order to facilitate exposure. It also raises the question whether this method may not prove a simple and successful one in cases of old ununited fractures of the clavicle.

CONCLUSIONS

1. Experiences are reported in 4 cases of clavicular resection in which rapid and complete restoration of bony continuity followed replacement in the periosteal bed of bone chips which were obtained from the excised portion of the clavicle.

2. The usefulness of this procedure in explorations requiring resection of a segment of clavicle is discussed as well as certain other possible applications of the method.

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EDITORIALS

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FEBRUARY, 1947

CANCER OF THE CERVIX

THE two papers appearing in this issue of SURGERY, GYNECOLOGY AND OBSTETRICS, describing the radiation reaction of cells seen in the vaginal secretion in cases of cervical carcinoma, represent a potential advance in the treatment of patients with this disease. The first paper concerns the distinguishing characteristics of cells exposed to radiation and their differentiation from unirradiated cells both normal and malignant. The second paper indicates a possible method of prognosis in cervical cancers under treatment by radiation. While the patient is still receiving radiation treatment, by examination of the vaginal secretion with special attention to the presence or absence of radiation reaction in the normal cells, a prognosis on the ultimate success of the treatment may apparently be obtained. It may be of basic importance that changes in the *normal* cells rather than disappearance of the malignant cells is the significant factor in prognosis. Patients in whom malignant cells were found to persist in the smear for some time nevertheless did well if the normal cells showed an adequate response to radiation; on the other hand those patients in whom the normal cells showed no response to radiation did poorly, even though the malignant cells disappeared.

Though admittedly the follow-up on this series is too short to justify a final conclusion as to the ultimate prognostic value of the vaginal smear in irradiated cases, nevertheless the early work of Gluecksmann and Spear on the one hand and of Warren, Meigs, and associates on the other hand would substantiate Graham's observations.

If after a longer period of follow-up this method still offers the same prognostic accuracy, another definite forward step in the treatment of cervical cancer will have been established. Heretofore it has not been uncommon to find, after what was believed to be a satisfactory clinical response to radiation, that cancer nevertheless recurred. Until now there has been no practical way of determining the response to radiation at the time of treatment. In patients showing minimal response to radiation by vaginal smear it is possible that roentgen therapy should be abandoned and a surgical attack attempted.

In the past few years the attitude toward radical surgery for carcinoma of the cervix has undergone considerable modification. It is recognized that simple total hysterectomy is not the proper operation. Metastases to lymph nodes may occur early in the disease and therefore this operation is not adequate. Taussig and Bonney have shown that the surgical removal of lymph nodes may cure 1

of 5 patients. Taussig's operation for the transperitoneal removal of nodes after radiation treatment of the local cervical growth has proved satisfactory in the hands of both Taussig and Morton. Recently at the Massachusetts General Hospital and the Pondville Hospital, a retroperitoneal operation has been advocated for the removal of these nodes and this approach has been found more satisfactory than the transperitoneal method of Taussig. The radical surgical operation has been proved to be safe, for in our hands one hundred patients have been operated upon without a single postoperative death. The bugbear of ureteral fistula has been overcome by greater care in preservation of the ureter's blood supply.

If Graham's work is corroborated the surgeon is offered an opportunity in radiation resistant cases to operate, rather than wait upon the results of radiation as he has had to do in the past. Radical operation in this group of patients may salvage a certain percentage that would otherwise be lost. Another possibility is that by the use of the vaginal smear during radiation treatment the radiologist may be able to increase the dosage of radiation in certain resistant cases.

Advances in methods of radiation treatment have also been made and Merritt's work, on the use of the vaginal cone, has been corroborated and advanced by Behney. In a disease for which progress in treatment seemed almost at a standstill ten years ago the outlook is more encouraging. Early diagnosis of cancer of the cervix by vaginal smear, as described by Papanicolaou; together with the possible selection of proper cases for radiation or surgery—as suggested by Graham's work—constitute two definite advances in the control of cervical cancer.

JOE VINCENT MEIGS.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE second edition of Mason and Zintel's *Preoperative and Postoperative Treatment*[1] is a well balanced monograph concerned with the modern care of the surgical patient. Its greatest value will be for the younger men entering on their surgical service.

The new edition is divided into the general conditions which concern all surgical patients and considerations of the regional and special divisions of surgery. The chapters on care of the cardiac, hypertensive, and diabetic patients are excellent. Others, as the sections on anestheisa and treatment of shock, are very brief and limited in their scope and give only a superficial summary of these subjects.

The indications for use of blood, the technique of typing and discussions of blood grouping are practical and concise. Postoperative pulmonary complications are presented in an excellent manner. The section on the care of superficial burns is mainly devoted to the triple dye treatment, and the use of antibiotics is only mentioned in a casual manner. The bibliography of this chapter is brief and contains only one reference as recent as 1944, four of 1943, and the remaining fourteen to papers written before the war.

The chapters devoted to the surgical specialties or specific regions of the body are generally good, and the methods advocated are sound. The sections devoted to the care of the thyroid patient and that on thoracic conditions are practical and broad in their scope; other sections, as those on stomach and small intestine, are brief and rather superficial. The chapters on physical medicine and trauma are of little value to a student desiring detailed information on these subjects.

The volume is well illustrated and most chapters include a satisfactory bibliography. The appendix is a helpful guide to the laboratory findings in blood and urine in health and disease. HARVEY S. ALLEN.

HIS thorough knowledge of electrocardiography is clearly reflected in the extensively revised and expanded second edition of Doctor Katz's book *Electrocardiography*[2]. The volume deals rather completely with the entire subject and is one of the best single volumes yet presented on this still young subject. The book is divided into three sections, the first dealing with the theory of electrocardiography, the second with a description of the normal electrocardiogram and the tracings characteristic of many pathological conditions and toxic states, and the third section dealing with a description of the arrhythmias.

Of the three sections, the first is probably the most difficult to read and understand and some beginners will no doubt become a little discouraged in trying to master this material. The text, however, in the second and third section is to be recommended even though at times the discussion tends to become verbose. The handling of the subjects, ventricular strain, coronary insufficiency, and digitalis effect, with the differential diagnosis of each, is excellent.

Doctor Katz makes three noticeable exceptions in terminology from that recommended by the American Heart Association. They are the use of axis shift instead of deviation, intraventricular block instead of bundle branch block, and the use of first and second degree arteriovenous block instead of incomplete block and incomplete block with dropped beats. These deviations will no doubt be criticized by other authorities on the subject.

The evolution of the electrocardiogram in recent myocardial infarction is exceedingly well presented and illustrated and will be of great value to the beginner as well as the advanced student. Doctor Katz is not in favor of the use of exercise tests, etc. in the attempt to diagnose transitory coronary insufficiency. The subject of interference and dissociation remains a difficult subject for the average student to master and a difficult subject for Doctor Katz to present. If the reader, however, will carefully read and reread this chapter he will have, certainly, a fairly good understanding of these complex arrhythmias.

"Summary tables" are used throughout the second and third sections which concisely present the salient features of normal and abnormal deflections of specific patterns and of various arrhythmias. The author points out in his preface that these will be of value to the beginner, indeed, even many of the so-called advanced students will welcome these tables.

The electrocardiograms are numerous, excellent, and described in detail. However, it is unfortunate that in many instances the print is so small that reading these descriptions is difficult. There is an extensive bibliography at the end of each section which adds greatly to the value of this work to the advanced student.

[1] PREOPERATIVE AND POSTOPERATIVE TREATMENT. Edited by Lt. Col. Robert L. Mason, M.C., A.U.S., and Harold A. Zintel, M.D. 2d ed. Philadelphia and London: W. B. Saunders Co., 1946.

[2] ELECTROCARDIOGRAPHY; INCLUDING AN ATLAS OF ELECTROCARDIOGRAMS. By Louis N. Katz, A.B., M.A., M.D., F.A.C.P. 2d rev. ed. Philadelphia: Lea & Febiger, 1946.

If the physician is going to own only one book on electrocardiography, this is probably the best one to have at this time. It would be of value, I believe, if Doctor Katz would write a small volume on electrocardiography solely for the beginner.

JOHN A. MART.

THE companion volume of Doctor Katz's book on electrocardiography has also been re-edited, revised, and expanded. *Exercises in Electrocardiographic Interpretation*[1] presents 100 selected cases with their accompanying electrocardiograms. The author describes his approach to an unknown cardiogram and then proceeds carefully to interpret the 166 electrocardiograms presented and to correlate his interpretation with the clinical story. This book thus makes available to the beginner, a carefully selected series of electrocardiograms representing many different but frequently encountered tracings; the beginner thus has the opportunity of comparing his own interpretations with those of Doctor Katz. This book will be of particular value to the physician who is attempting to learn electrocardiography without personal supervision. JOHN A. MART.

THE author of *Diseases of the Retina*[2] presents his book to the internist, pediatrician, and the neurologist as well as to the ophthalmologist. He has emphasized the general advance in medical knowledge by presenting retinal diseases in relation to systemic disorders. The present understanding of factors involved in arterial hypertension are presented according to the conception of Ricker who gives three stages of reaction, depending on the action of the agents on the vasomotor nerves: (1) simple or active hyperemia; (2) hyperemia with slowing of the blood stream; (3) stasis or cessation of the blood stream and the associated mechanical and chemical changes in the tissue.

It is a comprehensive presentation and divided into eight parts: (1) diseases of the retina resulting from disturbances in circulation; (2) diseases of the retina resulting from vascular malformations; (3) degenerative diseases of the retina on a hereditary basis; (4) inflammatory diseases of the retina; (5) tumors of the retina; (6) diseases of the retina leading to retinal detachment; (7) developmental anomalies of retina; (8) radiation injuries of the retina.

A bibliography is given after each chapter and treatment of the various conditions discussed is considered. It is a volume to be desired by students and teachers. BEULAH CUSHMAN.

THE clinical investigation and management of the sterile patient is not always carried out with sufficient thoroughness by the medical profession as a whole. This lack is undoubtedly due to the fact that discussions of the many varied factors are so widely scattered in the literature that one finds it difficult to summarize all of them, to evaluate them properly, and translate them into an organized plan that can be followed. The book *Diagnosis in Sterility*[3] compiles in one unit the essential features of this problem.

The important and frequent part that the male plays in instances of sterility is stressed. Studies of the semen are fully described and evaluated. The histology of the testicular tissue obtained by biopsy is correlated with the semen findings.

The section dealing with the endometrium presents a complete and excellent review of the present day knowledge of that tissue.

Other chapters consider history taking of infertile couples, basal temperature studies, tubal patency tests, postcoital examination of cervical mucus, and pelvic congestion.

This book offers a ready source from which one can prepare a procedure for the investigation and treatment of sterility. Such a procedure is the first essential of proper treatment.

HAROLD O. JONES and JOHN I. BREWER.

LIKE all Gaul, *Diagnostic Examination of the Eye*[4] by Conrad Berens and Joshua Zuckerman is divided into three parts, and like Gaul a complete territory is covered by those Caesar-like conquerers of ophthalmology, the distinguished, energetic, and tireless authors. The result is a volume that is unique in its conception, awesome in its scope, comprehensive in its contents, and noble in its versatility. All of this is within 711 pages of attractive print, pertinent illustrations, good diagrams, and encyclopedic detail. Like an encyclopedia, it is not devised for reading for pleasure, although there is much in it that gives pleasure. Rather it is to be used with profit, as a reference or guide book, as an outline to be followed in the development of a clinical sense, as an instrument to develop ophthalmic canniness, and as a reference to turn to when something goes awry.

The first two parts outline a step by step procedure that is designed to develop a systematic, almost instinctive, methodical approach to the solution of a patient's ophthalmic problem. Part one takes one through a routine of examination during the patient's first visit (13 steps). It begins with the interrogation of the patient and ends with the filling in of the record with information that is the result of this methodical examination. As one climbs the stairs to the rear of the orbit and from thence to the rear of the brain, neat signs of differential diagnostic import are at hand, like the advertisements one sees on the walls of escalators in the London underground. As might be expected by those who know the authors and their main interest, the chapter on motor function (the 6th step) is outstanding and note-

[1] EXERCISES IN ELECTROCARDIOGRAPHIC INTERPRETATION. By Louis N. Katz, A.B., M.A., M.D., F.A.C.P. 2d rev. ed. Philadelphia: Lea & Febiger, 1946.

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[4] DIAGNOSTIC EXAMINATION OF THE EYE. By Conrad Berens, M.D., F.A.C.S., and Joshua Zuckerman, M.D., C.M., F.A.C.S. Philadelphia: J. B. Lippincott Co., 1946.

worthy; perhaps the best of its kind in any of our ophthalmic textbooks.

Part two (examination during the second or final visit) embraces the postcycloplegic test, and other special tests that are particularly indicated such as those for color vision, fusion sense and depth perception, perimetry, and so on.

The details of each step are meticulously outlined and adequately described so that one can have no excuse in not understanding exactly what one is doing and how one is doing it. The final step (20) is a summary outline for findings, diagnosis, advice, treatment, progress, and results. It would, in the hands of ordinary mortals, write finis to a good piece of work.

But the authors, in Part three, have given us some of the most valuable and useful information to be found in the entire volume. Special methods of examination are plainly described. Supplementary instruments are taken apart before our eyes and we are told how to use, adjust, and fix them, too.

Only men of great experience and wise judgment, who are masters of organized thinking, could have given us this inestimable volume for our daily use and advantage. And, while it was written for the ophthalmologist, his assistants and students, the general surgeon and internist will get pleasure out of looking into its pages and will gain a new concept of and respect for the magnitude of ophthalmology.

DERRICK VAIL.

THE book, *The Principles of Neurological Surgery*[1] by Loyal Davis, with 192 engravings, containing 348 illustrations and 5 plates, 4 in color, is a modern textbook dealing with all phases of neurological surgery. It is compact, profusely illustrated, and its material is well balanced.

The third edition follows the same general plan as previous editions, but additions and refinements are evident throughout this volume. The first chapter, dealing with basic neurology and methods of examination has been greatly improved, and it contains much more information for the medical student and general practitioner for whom the book was written. Subsequent chapters deal with practically every disease of neurosurgical interest, and each is discussed briefly, but, for the most part, adequately, not only from the standpoint of diagnosis and treatment, but also from the point of view of results. This information is factual and reflects the critical attitude and mature judgment of the author.

Subjects of general interest, such as lesions of intervertebral discs, peripheral vascular disease, and surgical treatment of hypertension, are presented with such clarity that the reader should have little or no trouble selecting cases suitable for neurosurgical treatment.

Outstanding among Dr. Davis' numerous contributions to neurological surgery are his studies relating to injuries of peripheral nerves. This, together with the fact that during World War II he was an overseas consultant in neurological surgery, made it possible for him to include in this new edition an authoritative and up to date discussion, not only of lesions of peripheral nerves, but of traumatic lesions of the nervous system in general.

Perhaps it is the duty of a reviewer to be critical, but I have only praise for this book. It is an outstanding contribution to the teaching of medical students and house officers, and it provides information ideally arranged for the busy physician and surgeon whose work often requires some knowledge of the now broad field of neurological surgery.

W. GAYLE CRUTCHFIELD.

IN the form of an ample series of pictures of gross anatomical structures, Professor Jamieson's *Illustrations of Regional Anatomy*[2], is a very serviceable teaching aid. There is no accompanying text, and there are no directions designed to guide the dissector. The legends are of the briefest order. To the current edition the author has added an index and several new figures.

The illustrations are grouped in seven compact volumes. In each of the sections the loose leaves are fitted on pillars from which they are easily removable for rearrangement in any sequence which may meet the momentary need of the student. The pages are printed on one side only; the paper stock is unusually good.

The 305 illustrations cover the anatomy of the several subdivisions of the body: central nervous system, head and neck, abdomen, pelvis, thorax, upper limb, and lower limb. The head and neck are allotted the largest number of figures, the thorax the smallest number.

The brain is extensively illustrated in sections; basal nuclei, motor and sensory areas are indicated diagrammatically, as are also the principal tracts, commissures, etc.; blood vessels, cerebral ventricles, and choroid plexuses are all presented with profuse coloring.

The head and neck are illustrated by drawings which include entire dissection fields, laminar dissections of individual sense organs, diagrammatic representations of nerve plexuses, and transverse and sagittal sections. Some of the figures would be baffling to a beginner, since they do not indicate what has been excluded or which layers have been removed to bring into view the stratum which the figure portrays. Others lose value by being so diagrammatic that they merely suggest, but do not closely resemble, the structure as it appears in the human body.

The section on the abdomen contains ingeniously diagrammatic illustrations of the abdominal muscles and the inguinal canal, but some of them sacrifice

[1] THE PRINCIPLES OF NEUROLOGICAL SURGERY. By Loyal Davis M.S., M.D., Ph.D., D.Sc. (Hon.). 3rd rev. ed. Philadelphia: Lea & Febiger, 1946.

[2] ILLUSTRATIONS OF REGIONAL ANATOMY. By E. B. Jamieson, M.D. Section 1—CENTRAL NERVOUS SYSTEM. Section 2—HEAD AND NECK. Section 3—ABDOMEN. Section 4—PELVIS. Section 5—THORAX. Section 6—UPPER LIMB. Section 7—LOWER LIMB. 6th ed. Edinburgh: E. & S. Livingstone Ltd., 1946.

anatomical clarity for schematic vividness. The treatment of the inguinal region, mesenteries, blood vessels, kidneys, and suprarenals is highly conventional, resembling models rather than dissections themselves.

The schematic drawings of the abdominal layers are architectural achievements, but take considerable liberty with the true constitution of the parietal laminae.

In the volume on the pelvis and perineum color is again lavishly and helpfully used, but the author's order of plates is seemingly quite haphazard for a section of anatomy in which a knowledge of serial succession is of the fundamental importance. While the layers of the pelvic and urogenital diaphragms are shown in schematic clearness, they are not portrayed accurately: fascial layers of the perineum are shown in disjunction, not as strata continuous with layers in adjacent regions; the relations of the pelvic viscera to their ligamentous, fascial, and diaphragmatic supports would be of little use in training critical students for the practice of gynecology, urology, or proctology.

In the series of plates depicting the anatomy of the thorax, the schematic method is utilized to greater advantage, since much of the important anatomy of the thoracic cage and of its visceral, vascular, and nervous contents may be taught from transverse and sagittal sections and from surface projections of organs.

In the sections on the upper and lower extremities, the figures which show the areas of muscular attachment on the bones are fundamentally similar to those found in the standard textbooks, atlases, and manuals of gross anatomy. Here the order is the logical one of successive layers, from cutaneous nerves, superficial veins, and fascial sleeves, through progressively deeper layers of muscle. In the simpler figures, for example, those dealing with the synovial sheaths of the hand and foot, the schematic plan is utilized to great advantage; but when the same device is employed to show the tendons, nerves, vessels, and muscles, the collection of transected structures forms a somewhat bewildering assemblage.

The colors employed in the illustrations seem unnecessarily garrish. However, the reader cannot blame either the author or illustrator for indulging in such innocent gaiety, when chromatic feasts of this nature are so rare in the staid history of anatomic illustration.

Taken as a whole, *Illustrations of Regional Anatomy* is a useful adjunct to the student's regular anatomical library; it treats of the kind of anatomy which is customarily presented in charts. Its graphic character is analytical of the standard type illustration or take-apart models found in all fully equipped laboratories. The volumes of figures serve as a link between the standard atlas which the student uses at the dissection table and the blackboard drawings which are regularly a feature of the lecture in gross anatomy.

BARRY ANSON.

IN the 200 hundred page monograph *Early Ambulation and Related Procedures in Surgical Management*[1] by Leithauser the author reviews the history and development of early ambulation, making no claim for priority. Early ambulation as described consists in requiring the patient to be out of bed for standing, coughing, and walking at frequent intervals starting from 4 to 8 hours after operation. These brief periods of activity are separated by longer periods of rest flat in bed. Profound shock, uncontrolled hemorrhage, imminent death, rectus muscle incisions, and improperly closed incisions are believed to be the only contraindications to this type of treatment.

Pulmonary, circulatory and gastrointestinal complications are discussed in some detail and are believed to be eliminated or reduced by early ambulation. Psychological and economic advantages accrue under this management.

The author's routine care is described, including types of incision, suture material, and wound closure believed essential if early ambulation is to be used. His personal experience in the case of 2,047 patients in whom early ambulation was used is summarized. These reports are wholly favorable and a strong argument is made for this type of management.

Many surgeons will find objection to early ambulation in such cases as active peritonitis or empyema of the gall bladder. The method, however, deserves the careful study of all surgeons.

THOMAS C. DOUGLASS.

THE moderately sized book *Treatment of Bronchial Asthma*[2] is written by many authors. It is made up of 23 chapters, some of which are excellent and some quite inadequate. The outstanding chapters are probably those on the history of bronchial asthma, statistics, anatomy and physiology, house dust, pollen and fungi, food allergy, parasites, psychogenic factors, differential diagnosis, surgical treatment, complications and cardiac asthma.

The "Treatment of Bronchial Asthma," the title of the book, is hardly adequate. The information given is accurate but insufficient. Indications and directions for treatment are not clear enough for the general practitioner or medical student. It is unfortunate that there are no case reports, and that although directions for treatment of patients allergic to pollens or house dust are given, practically nothing is said about those allergic to horse dander, cottonseed, farm dusts, and other important causes of asthma. The use of tetanus toxoid is not mentioned. By including these omissions in a second edition, this book would be a "must" in the library of all interested in asthma and related subjects.

LEON UNGER.

[1] EARLY AMBULATION AND RELATED PROCEDURES IN SURGICAL MANAGEMENT. By Daniel J. Leithauser, M.D., F.A.C.S. Springfield, Ill.: Charles C. Thomas, 1946.

[2] TREATMENT OF BRONCHIAL ASTHMA. By Vincent J. Derbes, M.D., and Hugo T. Engelhardt, M.D., F.A.C.P. With chapters by 19 contributors. Philadelphia, London, Montreal: J. B. Lippincott Co., 1946.

FROM the University of Havana *Clinica y Laboratorio*[1] is a critical interpretation of the methods used in the clinical laboratory and the results thereof. Sections are devoted to all of the subjects usually considered in a work of this type. In addition, much space is given to the field of mycology. There are chapters on biopsies, allergy tests, and medical toxicology which are necessarily incomplete. An extensive bibliography refers to both the English and Spanish literature, and the author frequently appraises the value of the references listed.

Pittaluga's aim is to acquaint medical men with the value of the standard laboratory procedures, and he does not intend to describe in detail all of the methods discussed. When several methods are available for performing a given examination, he discusses their relative merits and expresses his preference. To aid the clinician in intelligent utilization of the laboratory, background material from the fields of physiology, biochemistry, and pathology is supplied.

This book is not to be regarded as a manual of laboratory procedure nor as a complete treatise on clinical pathology, but serves well its expressed purpose of acquainting the general medical man with the usefulness of the various clinical laboratory methods.

AURA P. DUKE.

THE compendium *The Chest*[2] by Dr. Leo Rigler provides a review of thoracic roentgen diagnosis and is likewise useful as an atlas for ready reference, since its 350 odd pages are replete with illustrations of superb clarity and photographic excellence.

The entire thorax is not included in specific detail; the heart and diaphragm, for example, are discussed only insofar as they are implicated in considerations of other thoracic viscera or regions. From the standpoint, however, of the physician or surgeon interested in chest diseases, the field is well covered.

Roentgen examination methods and techniques are concisely presented from the practical viewpoint of the needs of the clinician, the indications, advantages, and limitations of each means of study being given. A minimum of technical physical data is included.

Twenty-five pages are devoted to the "normal" chest, the anatomic variants or anomalies which may have no clinical significance are discussed, and numerous extraneous causes for the production of artefacts which should not be interpreted as intrathoracic lesions are pointed out. Thoracic physiology is briefly reviewed and the principles governing mediastinal shift and mediastinal movements, as in obstructive emphysema, are pointed out.

The pathologic conditions presented and discussed include principally those of the bronchi, lungs, mediastinum, and pleura. A brief, concise, general presentation of the subject matter in didactic style precedes the main feature in this volume, which is illustrative roentgenograms. A detailed description of these illustrations accompanies them on opposite pages.

If criticism is to be made of this work it would be in the arrangement of the didactic introductory material in its relation to the illustrations. They do not always follow the same scheme of presentation. For example, the discussion of the "normal chest" is interrupted at page 36 by numerous illustrations, to be resumed only on page 44. This factor is minimized by suitable annotations directing the reader to the proper page for preservation of continuity. Errors in the body of the subject matter might be pointed out but they are minor and not consistent.

This volume is beautifully printed, the roentgenograms are faultlessly reproduced, and to have secured such admirably clear cases for illustration and in such generous numbers is indeed remarkable. The purpose for which this material was compiled has been wholly satisfied.

HIRAM T. LANGSTON.

A VERY important book for general surgeons and gynecologists has been written by Richard Te Linde.[3] He has endeavored to describe nearly all methods of operative approach to gynecological conditions, simple and complicated. By using his own artist and also selecting the drawings from well illustrated articles by other operators he has covered the field beautifully. There are very few criticisms possible in a volume of this size and magnitude. The book is unquestionably up-to-date, and all new operative methods are well described and illustrated. It does not purport to be an atlas for besides the illustrations, both line drawings and half tones, there is an extensive text giving descriptions of the lesions, their symptoms, diagnosis, etiology, and treatment.

For the practitioner who is dependent upon textbooks for aid in attacking a given problem this book gives excellent advice, very satisfactory reviews of the current opinions, and sound advice as to procedures, with these are excellent illustrations of the surgical technique. In most texts of gynecology, satisfactorily illustrated operative technique is omitted but in this book operative technique is stressed.

This is an excellent book and one that can be recommended with great enthusiasm.

JOE V. MEIGS.

THE small monograph, *Diseases of the Basal Ganglia and Subthalamic Nuclei*[4] reprinted from the *Oxford Loose-Leaf Medicine*, has recently been published in attractive book form, and it is an up-to-date treatise on a very difficult subject by one of the country's best informed neurologists and investigators of neurologic problems. Anyone who would attempt an elucidation of the subject of disease of

[1] CLINICA Y LABORATORIO. By Dr. Gustavo Pittaluga. With the collaboration of Dr. Enrique Galan and Dr. Antonio Guernica. Havana, Cuba: M. V. Fresneda, 1946.

[2] THE CHEST; A HANDBOOK OF ROENTGEN DIAGNOSIS.. By Leo G. Rigler, M.D. Chicago, Ill.: The Year Book Publishers Inc., 1946.

[3] OPERATIVE GYNECOLOGY. By Richard W. Te Linde, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1946.

[4] DISEASES OF THE BASAL GANGLIA AND SUBTHALAMIC NUCLEI. By D. Denny-Brown, M.D., C.H.B., Dr. Phil.; F.R.C.P. Edited by Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). New York: Oxford University Press, 1946.

the basal ganglia must necessarily be not only a clear thinking person, but, more simply, a brave man. This work, after a brief consideration of the anatomy, physiology, and pathology of the basal ganglia in man, discusses individually, as to definition, etiology, history, symptoms, physical findings, course and treatment, the following diseases: paralysis agitans, progressive atrophy of the globus pallidus, the various forms of parkinsonism, hepatolenticular degeneration, dystonia musculorum deformans, the athetoid states, Huntington's chorea, and other forms of adult chorea. The discussion of hepatolenticular degeneration (Wilson's disease; progressive lenticular degeneration) is a particularly lucid and instructive one. Though the section dealing with this syndrome occupies only 21 pages, the reader is given full understanding of the clinical signs, and particularly of the pathological changes in the brain and liver. In that section, as throughout the book, the older, "basic" literature has been studied and quoted freely, as well as all the pertinent literature of a more recent date.

This reviewer is left not only with a clearer knowledge of the fundamental signs and changes in the disease states of the basal ganglia, but also with the rather depressing knowledge that while more and increasing information is added yearly to the fundamental approaches to the causes and effects of these diseases, there is still little that can be accomplished by either medical or surgical treatment.

This book is not easy reading. It is not one for the casual reader, but rather one for the student specifically interested in the subject. It can be used as source material not only because of the original content, but also because of the exhaustive bibliography which is appended. JOHN MARTIN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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A PRACTICAL HANDBOOK OF MIDWIFERY AND GYNAECOLOGY FOR STUDENTS AND PRACTITIONERS. By W. F. T. Haultain, O.B.E., M.C., B.A., M.B., B. Ch., F.R.C.P. Ed., F.R.C.S. Ed., F.R.C.O.G., and Clifford Kennedy, M.B., Ch.B., F.R.C.S. Ed., F.R.C.O.G. 3d ed. Baltimore: The Williams & Wilkins Co., 1946.

ENDOCRINE FUNCTION OF THE HYPOPHYSIS. By Harry B. Friedgood, M.D. Edited by Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). New York: Oxford University Press, 1946.

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CONDUCTION ANESTHESIA. Clinical Studies of George P. Pitkin, M.D., F.A.C.S., F.I.C.A. Edited by James L. Southworth, M.D., and Robert A. Hingson, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1946.

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SURGICAL TREATMENT OF THE SOFT TISSUES. Edited by Frederic W. Bancroft, A.B., M.D., F.A.C.S., and George H. Humphreys, II, A.B., M.D., Sc.D., F.A.C.S. Philadelphia, London, Montreal: J. B. Lippincott Co., 1946.

LEHRBUCH DER GYNAEKOLOGISCHEN DIAGNOSTIK FUER AERZTE UND STUDIERENDE. Von Dr. W. Neuweiler. Bern: Hans Huber, 1946.

ADOLESCENT STERILITY. By M. F. Ashley Montagu. Springfield, Illinois: Charles C Thomas, 1946.

HEALTH INSURANCE IN THE UNITED STATES. By Nathan Sinai, Dr. P. H. Odin W. Anderson, and Melvin L. Dollar. New York: The Commonwealth Fund, 1946.

THE X-RAY TREATMENT OF ACCESSIBLE CANCER. By D. Waldron Smithers, M.D., D.M.R. Baltimore: The Williams & Wilkins Co., 1946.

MYASTHENIA GRAVIS. By Dr. Adalberto R. Goñi. Baltimore: The Williams & Wilkins Co., 1946.

MUSCLE TESTING; TECHNIQUES OF MANUAL EXAMINATION. Lucille Daniels, Marian Williams, and Catherine Worthingham. Philadelphia and London: W. B. Saunders Co., 1946.

NURSING CARE IN CHRONIC DISEASES. Edith L. Marsh, R.N., S.C.M. Philadelphia: J. B. Lippincott Co., 1946.

OUTLINE OF CYSTOSCOPIC TECHNIC AND DIAGNOSIS. Geza Schinagel, M.D. Ann Arbor, Michigan: Edwards Brothers, Inc., 1946.

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A MANUAL OF TOMOGRAPHY. By M. Weinbren, B. Sc. (S.A.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), F.F.R. (Lond.), D.M.R.E. (Camb.). London: H. K. Lewis & Co., Ltd., 1946.

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